To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

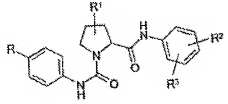
Title of Invention: Method for the production of pyrrolidine-1,2-dicarboxylic acid-1-(phenylC-amide)-2-(phenylC-amide)) Derivatives &

Inventors (please provide full names): Werner Medwski, Christos Tsaklakidis, Dieter Dorsch, Bertram Cezanne & Johannes Gleitz

Earliest Priority Date: 04/03/03 1-(phenylcarbamoyl)-pyrrolidine-2-carboxylic acid derivatives as intermediate

Listing of Claims:

1. (Original) Process for the preparation of compounds of the formula I



I

including mixtures thereof in all ratios, characterised in that

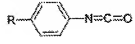
a) a compound of the formula II

II

in which

R^1 is as defined above,

is reacted with a compound of the formula III

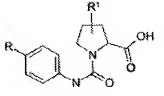


III

in which

R is as defined above,

to give a compound of the formula IV



IV

```
=> fil reg;dis his nofile;d l5 que stat;fil hcaplus;d 1-16 ibib abs fhit 16

FILE 'REGISTRY' ENTERED AT 15:39:04 ON 18 JUN 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
```

10551670

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 17 JUN 2008 HIGHEST RN 1028750-52-8
DICTIONARY FILE UPDATES: 17 JUN 2008 HIGHEST RN 1028750-52-8

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 9, 2008.

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

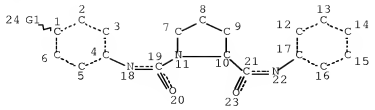
(FILE 'HOME' ENTERED AT 15:33:08 ON 18 JUN 2008)

FILE 'REGISTRY' ENTERED AT 15:33:26 ON 18 JUN 2008
L1 STR
L2 50 SEA SSS SAM L1
L3 STR L1
L4 47 SEA SSS SAM L3
L5 746 SEA SSS FUL L3
D L5 QUE STAT

FILE 'HCAPLUS' ENTERED AT 15:37:04 ON 18 JUN 2008
L6 16 SEA ABB=ON PLU=ON L5/P
D 1-16 IBIB ABS HITSTR

FILE 'REGISTRY' ENTERED AT 15:39:04 ON 18 JUN 2008

L3 STR



VAR G1=X/25
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 26

STEREO ATTRIBUTES: NONE
L5 746 SEA FILE=REGISTRY SSS FUL L3

100.0% PROCESSED 1364 ITERATIONS 746 ANSWERS
SEARCH TIME: 00.00.01

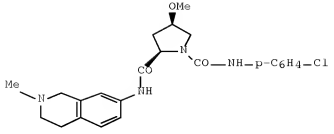
FILE 'HCAPLUS' ENTERED AT 15:39:04 ON 18 JUN 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 18 Jun 2008 VOL 148 ISS 25
FILE LAST UPDATED: 17 Jun 2008 (20080617/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> dis his 16-

     (FILE 'REGISTRY' ENTERED AT 15:33:26 ON 18 JUN 2008)

     FILE 'HCAPLUS' ENTERED AT 15:37:04 ON 18 JUN 2008
L6            16 S L5/P


=> d 16 1-16 ibib abs fhitstr

L6   ANSWER 1 OF 16  HCAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2007:1334447  HCAPLUS  Full-text
DOCUMENT NUMBER:          148:11474
TITLE:                    Synthesis of substituted prolinamides and their use as
                          Factor Xa and/or serine protease inhibitors
INVENTOR(S):              Gerlach, Kai; Priepke, Henning; Pfau, Roland; Wienen,
                          Wolfgang; Schuler-Metz, Annette; Dahmann, Georg; Nar,
                          Herbert
PATENT ASSIGNEE(S):       Boehringer Ingelheim International G.m.b.H., Germany;
                          Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
SOURCE:                   PCT Int. Appl., 106pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 German
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ----------          ----   --------    -------------------     --------
     WO 2007131982        A2    20071122    WO 2007-EP54631         20070514
     WO 2007131982        A3    20080110
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
             CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB,
             GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM,
             KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK,
             MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
             RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT,
             TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,
             GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
             BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
     US 20080139605       A1    20080612    US 2007-749204          20070516
PRIORITY APPLN. INFO.:                     EP 2006-113977      A   20060516
                                           EP 2007-102566      A   20070216
OTHER SOURCE(S):          MARPAT 148:11474
GI
```



I

AB Title compds., e.g. (I) as free bases or salts, were prepared as Factor Xa and/or serine protease inhibitors (no data) for treatment of medical disorders (no specified), and recipes for their delivery as ampuls for injection, tablets, capsules, or suppositories are given. Thus, I was prepared starting from (2R,4R)-4-methoxy-pyrrolidin-1,2-dicarbonic acid 1-(1,1-dimethyl)ethyl ester, 4-chloro-Ph isocyanate, and 1,2,3,4-tetrahydro-2-methyl-7-isoquinolinamine, in three steps by first deprotecting the acid group and condensing with the isocyanate, followed by amide formation with the remaining 2-position acid.

IT 957469-66-8P

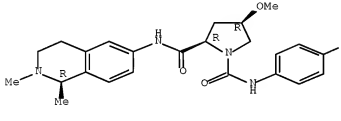
RL: PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of substituted prolinamides and their use as Factor Xa and/or serine protease inhibitors)

RN 957469-66-8 HCAPLUS

CN 1,2-Pyrrolidinedicarboxamide, N1-(4-bromophenyl)-4-methoxy-N2-[(1R)-1,2,3,4-tetrahydro-1,2-dimethyl-6-isoquinolinyl]-, (2R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN

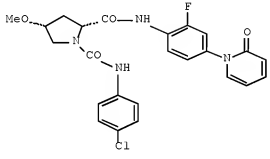
ACCESSION NUMBER: 2007:1004082 HCAPLUS Full-text

DOCUMENT NUMBER: 147:377578

TITLE: The discovery of (2R,4R)-n-(4-chlorophenyl)-n-(2-fluoro-4-(2-oxopyridin-1(2H)-yl)phenyl)-4-methoxypyrrolidine-1,2-dicarboxamide (PD 0348292), an orally efficacious factor Xa inhibitor

AUTHOR(S): Kohrt, Jeffrey T.; Bigge, Christopher F.; Bryant, John W.; Casimiro-Garcia, Agustin; Chi, Liguo; Cody, Wayne L.; Dahring, Tawny; Dudley, Danette A.; Filipski, Kevin J.; Haarer, Staci; Heemstra, Ron; Janiczek, Nancy; Narasimhan, Lakshmi; McClanahan, Thomas; Peterson, J. Thomas; Sahasrabudhe, Vaisheli; Schaum,

Robert; Van Huis, Chad A.; Welch, Kathleen M.; Zhang, Erli; Leadley, Robert J.; Edmunds, Jeremy J.
CORPORATE SOURCE: Michigan Laboratories, Pfizer Global Research & Development, Ann Arbor, MI, 48105, USA
SOURCE: Chemical Biology & Drug Design (2007), 70(2), 100-112
CODEN: CBDDAL; ISSN: 1747-0277
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

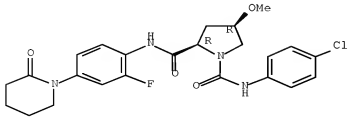
AB Herein, we report the discovery of novel, proline-based factor Xa inhibitors containing a neutral P1 chlorophenyl pharmacophore. Through the addnl. incorporation of 1-(4-amino-3-fluoro-phenyl)-1H-pyridin-2-one 22, as a P4 pharmacophore, we discovered compound 7 (PD 0348292, I). This compound is a selective, orally bioavailable, efficacious FXa inhibitor that is currently in phase II clin. trials for the treatment and prevention of thrombotic disorders.

IT 536746-98-2P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pyridinyl pyrrolidines as factor Xa inhibitors)

RN 536746-98-2 HCAPLUS

CN 1,2-Pyrrolidinedicarboxamide, N1-(4-chlorophenyl)-N2-[2-fluoro-4-(2-oxo-1-piperidinyl)phenyl]-4-methoxy-, (2R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:907918 HCAPLUS Full-text
DOCUMENT NUMBER: 147:257637
TITLE: Preparation of 2-pyrrolidinecarboxamides as factor Xa inhibitors
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Gmbh & Co. KG, Germany
SOURCE: Eur. Pat. Appl., 32pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1818330	A1	20070815	EP 2006-101653	20060214
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
WO 2007093595	A1	20070823	WO 2007-EP51390	20070213
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

PRIORITY APPLN. INFO.: EP 2006-101653 A 20060214
OTHER SOURCE(S): MARPAT 147:257637
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

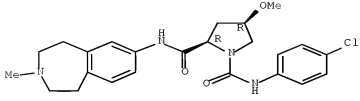
AB Title compds. I [K1, K2 = CH2, CO, etc.; K2, K3 = CH2, CO, etc.; X = S, O, CF2, etc.; A1 = N, CR10; A2 = N, CR11; A3 = N, CR12; R10, R11, R12 = H, halo, alkyl, etc.; R3 = H, alkyl; R5 = H, alkyl; R4 and R5 together = CO, CF2, etc.; R13 = H, alkyl; M = Ph, pyridyl, etc.; -L-E-G-J- = C-C-C-C, C-C=C-C] and their pharmaceutically acceptable salts and formulations were prepared For example, N-acylation of pyrrolidine II with 4-chlorophenylisocyanate afforded pyrrolidinecarboxamide III. Compds. I are claimed to be useful as factor Xa inhibitors.

IT 945755-66-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 2-pyrrolidinecarboxamides as factor Xa inhibitors)

RN 945755-66-8 HCAPLUS

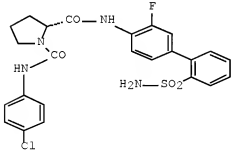
CN 1,2-Pyrrolidinedicarboxamide, N1-(4-chlorophenyl)-4-methoxy-N2-(2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepin-7-yl)-, (2R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:809018 HCAPLUS Full-text
DOCUMENT NUMBER: 147:291356
TITLE: Structure-based drug design of pyrrolidine-1, 2-dicarboxamides as a novel series of orally bioavailable factor Xa inhibitors
AUTHOR(S): Van Huis, Chad A.; Bigge, Christopher F.; Casimiro-Garcia, Agustin; Cody, Wayne L.; Dudley, Danette A.; Filipski, Kevin J.; Heemstra, Ronald J.; Kohrt, Jeffrey T.; Narasimhan, Lakshmi S.; Schaum, Robert P.; Zhang, Erli; Bryant, John W.; Haarer, Staci; Janiczek, Nancy; Leadley, Robert J., Jr.; McClanahan, Thomas; Peterson, J. Thomas; Welch, Kathleen M.; Edmunds, Jeremy J.
CORPORATE SOURCE: Michigan Laboratories, Pfizer Global Research & Development, Ann Arbor, MI, 48105, USA
SOURCE: Chemical Biology & Drug Design (2007), 69(6), 444-450 CODEN: CBDDAL; ISSN: 1747-0277
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB A novel series of pyrrolidine-1,2-dicarboxamides was discovered as factor Xa inhibitors using structure-based drug design. This series consisted of a neutral 4-chlorophenylurea P1, a biphenylsulfonamide P4 and a D-proline

scaffold (I, IC50 = 18 nM). Optimization of the initial hit resulted in an orally bioavailable, subnanomolar inhibitor of factor Xa (13, IC50 = 0.38 nM), which was shown to be efficacious in a canine electrolytic model of thrombosis with minimal bleeding.

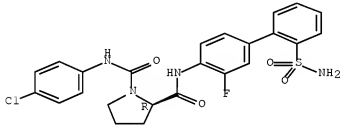
IT 536746-25-5P

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pyrrolidine dicarboxamides as orally bioavailable factor Xa inhibitors)

RN 536746-25-5 HCAPLUS

CN 1,2-Pyrrolidinedicarboxamide, N2-[2'-(aminosulfonyl)-3-fluoro[1,1'-biphenyl]-4-yl]-N1-(4-chlorophenyl)-, (2R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:1006402 HCAPLUS Full-text

DOCUMENT NUMBER: 145:377210

TITLE: Preparation of polymorphic crystalline forms of N1-(4-chlorophenyl)-N2-[2-fluoro-4-(2-oxo-1(2H)-pyridinyl)phenyl]-4-methoxy-(2R,4R)-1,2-pyrrolidinedicarboxamide factor Xa inhibitor

INVENTOR(S): Samas, Brian Matthew; Vrieze, Derek Clinton

PATENT ASSIGNEE(S): Warner-Lambert Company LLC, USA

SOURCE: PCT Int. Appl., 31pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006100565	A1	20060928	WO 2006-IB633	20060313

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,

CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

AU	2006226043	A1	20060928	AU 2006-226043	20060313
CA	2602550	A1	20060928	CA 2006-2602550	20060313
EP	1891044	A1	20080227	EP 2006-727345	20060313
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
JP	2006265254	A	20061005	JP 2006-81926	20060324
IN	2007DN06355	A	20070831	IN 2007-DN6355	20070816
KR	2007107156	A	20071106	KR 2007-721901	20070921
CN	101146792	A	20080319	CN 2006-80009365	20070921

PRIORITY APPLN. INFO.: US 2005-664870P P 20050324
WO 2006-IB633 W 20060313

OTHER SOURCE(S): CASREACT 145:377210

AB Polymorphic crystalline forms of N1-(4-chlorophenyl)-N2-[2-fluoro-4-(2-oxo-1(2H)-pyridinyl)phenyl]-4-methoxy-(2R,4R)-1,2-pyrrolidinedicarboxamide factor Xa inhibitor are prepared and characterized by their powder X-ray diffraction, solid-state NMR, etc., and pharmaceutical dosage forms containing it are claimed.

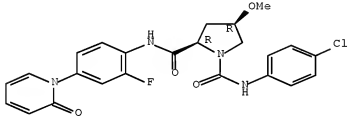
IT 536748-46-6P

RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of polymorphic crystalline forms of N1-(4-chlorophenyl)-N2-[2-fluoro-4-(2-oxo-1(2H)-pyridinyl)phenyl]-4-methoxy-(2R,4R)-1,2-pyrrolidinedicarboxamide factor Xa inhibitor)

RN 536748-46-6 HCAPLUS

CN 1,2-Pyrrolidinedicarboxamide, N1-(4-chlorophenyl)-N2-[2-fluoro-4-(2-oxo-1(2H)-pyridinyl)phenyl]-4-methoxy-, (2R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

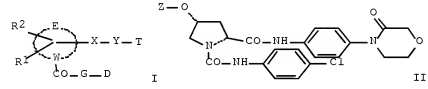
L6 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2006:316811 HCAPLUS Full-text
DOCUMENT NUMBER:	144:370085
TITLE:	Preparation of 1,2-pyrrolidinedicarboxamides as coagulation factor Xa inhibitors
INVENTOR(S):	Cezanne, Bertram; Dorsch, Dieter; Mederski, Werner; Tsaklakidis, Christos; Gleitz, Johannes
PATENT ASSIGNEE(S):	Merck Patent G.m.b.H., Germany
SOURCE:	PCT Int. Appl., 103 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	German

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006034769	A1	20060406	WO 2005-EP9418	20050901
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
DE 102004047254	A1	20060413	DE 2004-102004047254	20040929
AU 2005289164	A1	20060406	AU 2005-289164	20050901
CA 2581732	A1	20060406	CA 2005-2581732	20050901
EP 1797071	A1	20070620	EP 2005-790356	20050901
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
CN 101031561	A	20070905	CN 2005-80032789	20050901
JP 2008514655	T	20080508	JP 2007-533891	20050901
MX 200703470	A	20070510	MX 2007-3470	20070323
KR 2007057878	A	20070607	KR 2007-707053	20070328
US 20080081814	A1	20080403	US 2007-576207	20070328
IN 2007KN01474	A	20070720	IN 2007-KN1474	20070425
PRIORITY APPLN. INFO.:			DE 2004-102004047254A	20040929
			WO 2005-EP9418 W	20050901

OTHER SOURCE(S): MARPAT 144:370085
GI



AB Title compds. I [R1, R2 = H, =O, halo, etc.; R3 = H, CH2CH(OH)CH2OH, CH2CH(OH)CH2NH2, etc.; W = N, CR3 with provisos, etc.; E = together with W form a 3 to 7-membered hetero or carbocyclic ring with provisos; D = bond, double bond, etc.; G = [C(R4)2]n, [C(R4)2]nNR3, [C(R4)2]nO, etc.; R4 = H, A; A =alkyl with provisos; X = [C(R4)2]nCONR3[C(R4)2]n, etc.; n = 0-2; Y = alkylene, cycloalkylene, etc.; T = bond, double bond, heterocycle with provisos, etc.] and their pharmaceutically acceptable salts and formulations were prepared For example, O-acylation of hydroxypyrrolidine II [Z = H] afforded pyrrolidinedicarboxamide II [Z = CO2Et]. In coagulation factor Xa inhibition assays, pyrrolidinedicarboxamide II [Z = CO2Et] exhibited an IC50 value of 2.0x10-9 M.

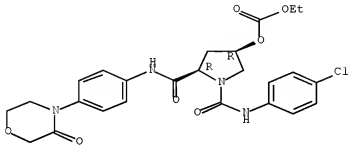
IT 882066-89-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrrolidinedicarboxamides as coagulation factor xa inhibitors)

RN 882066-89-9 HCAPLUS

CN Carbonic acid, (3R,5R)-1-[[(4-chlorophenyl)amino]carbonyl]-5-[[[4-(3-oxo-4-morpholinyl)phenyl]amino]carbonyl]-3-pyrrolidinyl ethyl ester (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:273940 HCAPLUS Full-text

DOCUMENT NUMBER: 144:331461

TITLE: Drugs containing carbonyl compounds and their use for the prophylaxis and/or therapy of thromboembolic illnesses

INVENTOR(S): Cezanne, Bertram; Dorsch, Dieter; Mederski, Werner; Tsaklakidis, Christos; Gleitz, Johannes

PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany

SOURCE: Ger. Offen., 77 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 102004045796	A1	20060323	DE 2004-102004045796	20040922
AU 2005287637	A1	20060330	AU 2005-287637	20050824
CA 2581172	A1	20060330	CA 2005-2581172	20050824
WO 2006032342	A2	20060330	WO 2005-EP9124	20050824
WO 2006032342	A3	20070111		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

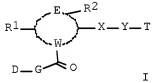
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ,

CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

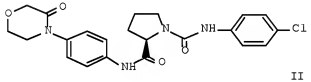
EP 1791597	A2	20070606	EP 2005-774750		20050824
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU					
CN 101102818	A	20080109	CN 2005-80031723		20050824
JP 2008513387	T	20080501	JP 2007-531628		20050824
MX 200703175	A	20070518	MX 2007-3175		20070316
KR 2007054210	A	20070528	KR 2007-706440		20070321
US 20080003214	A1	20080103	US 2007-575711		20070321
IN 2007KN01362	A	20070720	IN 2007-KN1362		20070418
PRIORITY APPLN. INFO.:			DE 2004-102004045796A		20040922
			WO 2005-EP9124	W	20050824

OTHER SOURCE(S): MARPAT 144:331461

GI



I



II

AB Use of heterocyclic carbonyl compds. I [R1, R2 = H, :O,,halogen, A, C.tplbond.CH, OR3,N(R3)2, NO2, CN, N3, CO2R3, CON(R3)2, [C(R4)2]n-Ar, [C(R4)2]n-heterocyclyl, [C(R4)2]n-cycloalkyl, OC(:O)R3, OC(:O)N(R3)2, NR3COA, NR3SO2A; R1R2 = bi- or spirocyclic 3- to 7-membered carbocycle or heterocycle (containing 0 - 3 N, O, or S); R3 = H, A, CH2C.tplbond.CH, CH2CH(OH)CH2OH, CH2CH(OH)CH2NH2, CH2CH(OH)CH2-heterocycle, [C(R4)2]n-Ar, [C(R4)2]n-heterocyclyl, [C(R4)2]n-cycloalkyl, [C(R4)2]n-CO2A, [C(R4)2]nN(R4)2; R4 = H, A; EW = 3- to 7-membered carbocycle or heterocycle (containing 0 - 3 N, O, or S); W = N, CR3, sp2-C; D = mono- or binuclear, (un)substituted aromatic carbocycle or heterocycle (containing 0 - 3 N, O, or S); G = [C(R4)2]n, [C(R4)2]n-NR3, [C(R4)2]nO, [C(R4)2]nS, [CR4:CR4]n; X = [C(R4)2]nCONR3[C(R4)2]n, [C(R4)2]nNR3CO[C(R4)2]n, [C(R4)2]nNR3[C(R4)2]n, [C(R4)2]nO[C(R4)2]n, [C(R4)2]nC(:O)[C(R4)2]n, [C(R4)2]nCO2[C(R4)2]n; Y = alkylene, cycloalkylene, heterodiyl, aryldiyl; T = mono- or binuclear, (un)substituted aromatic carbocycle or heterocycle (containing 0 - 3 N, O, or S); A = (un)branched C1-10-alkyl (optionally containing, O, S or CH:CH in the chain and replacing 1 - 7 H with F); n = 0 - 2; o = 1 - 3], their derivs., solvates, salts and stereoisomers, for the prophylaxis and/or therapy of thromboembolic illnesses. Thus, proline derivative II was prepared from N-Boc-D-proline via amidation with 4-(4-aminophenyl)morpholin-3-one in DMF containing 1-hydroxybenzotriazole hydrate, N-[3-(dimethylamino)propyl]-N'-

ethylcarbodiimide hydrochloride and N-methylmorpholine, N-deprotection with aqueous HClin dioxane and carbamylation with 4-ClC6H4NCO in CH2Cl2 containing Et3N. The receptor binding activity of II was determined [IC50 = 1.8 x 10-8 M vs. FXa; IC50 = 2.3 x 10-8 M vs. TF/FVIIa].

IT 536747-22-5P

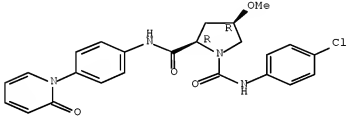
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drugs containing carbonyl compds. and their use for the prophylaxis and/or therapy of thromboembolic illnesses)

RN 536747-22-5 HCAPLUS

CN 1,2-Pyrrolidinedicarboxamide, N1-(4-chlorophenyl)-4-methoxy-N2-[4-(2-oxo-1(2H)-pyridinyl)phenyl]-, (2R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:1075769 HCAPLUS Full-text

DOCUMENT NUMBER: 143:347450

TITLE: Synthesis of prolinyl derivatives for use in the treatment of thromboembolic diseases or tumors

INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes

PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany

SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

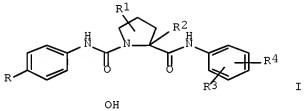
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005092849	A1	20051006	WO 2005-EP2306	20050304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 102004014945	A1	20051013	DE 2004-102004014945	20040326
AU 2005225489	A1	20051006	AU 2005-225489	20050304

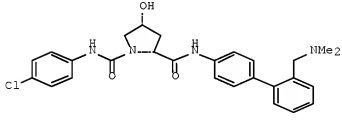
CA 2561057	A1	20051006	CA 2005-2561057		20050304
EP 1735279	A1	20061227	EP 2005-715737		20050304
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, LV					
CN 1938269	A	20070328	CN 2005-80009735		20050304
BR 2005009174	A	20070918	BR 2005-9174		20050304
JP 2007530469	T	20071101	JP 2007-504284		20050304
IN 2006KN02397	A	20070525	IN 2006-KN2397		20060824
MX 2006PA10771	A	20061215	MX 2006-PA10771		20060920
KR 2007010131	A	20070122	KR 2006-719772		20060925
US 20070135507	A1	20070614	US 2006-594024		20060925
PRIORITY APPLN. INFO.:			DE 2004-102004014945A		20040326
			WO 2005-EP2306	W	20050304

OTHER SOURCE(S): MARPAT 143:347450

GI



I



II

AB The invention relates to title compds., e.g. (I), which are inhibitors of coagulation factors Xa and VIIa and can be used for the prophylaxis and/or treatment of thromboembolic diseases and for the treatment of tumors (no data). Thus, (II) was prepared by condensation of (2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxylic acid 1-tert-Bu ester with 4'-amino-N,N-dimethyl-[1,1'-biphenyl]-2-methanamine, followed by condensation with 4-nitrophenyl chloroformate and 4-chloroaniline, to give II (no yield). Sixteen title compds. are claimed, and formulations for administration (e.g., injections, suppositories, etc.) are given.

IT 865853-86-7P

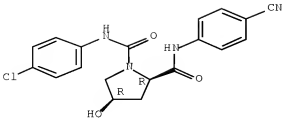
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of proline derivs. for treatment of thromboembolic diseases or tumors)

RN 865853-86-7 HCAPLUS

CN 1,2-Pyrrolidinedicarboxamide, N1-(4-chlorophenyl)-N2-(4-cyanophenyl)-4-hydroxy-, (2R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

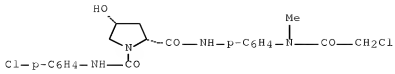
L6 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:564637 HCAPLUS Full-text
DOCUMENT NUMBER: 143:97636
TITLE: Synthesis of prolinylarylacetamides as coagulation factor Xa inhibitors for use in the prevention or treatment of thromboembolic diseases or tumors
INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005058817	A1	20050630	WO 2004-EP13509	20041126
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10358814	A1	20050721	DE 2003-10358814	20031216
AU 2004299197	A1	20050630	AU 2004-299197	20041126
CA 2549589	A1	20050630	CA 2004-2549589	20041126
EP 1697318	A1	20060906	EP 2004-820404	20041126
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
CN 1894210	A	20070110	CN 2004-80037698	20041126
BR 2004017630	A	20070327	BR 2004-17630	20041126
JP 2007513988	T	20070531	JP 2006-544256	20041126
IN 2006KN01579	A	20070504	IN 2006-KN1579	20060608
MX 2006PA06740	A	20060818	MX 2006-PA6740	20060614
US 20070185189	A1	20070809	US 2006-583094	20060615

PRIORITY APPLN. INFO.: DE 2003-10358814 A 20031216
WO 2004-EP13509 W 20041126

OTHER SOURCE(S): MARPAT 143:97636

GI



I

AB Title compds., e.g. (I), are claimed as inhibitors of coagulation factor Xa and are claimed for use for the prophylaxis and/or therapy of thromboembolic diseases and in the treatment of tumors, as well as kits containing the compds. of interest. Thus, the title compds. were prepared, e.g., by condensation of (2R,4R)-1-(4-chlorophenylcarbamoyl)-4- hydroxyproline and N-(4-aminophenyl)2-dimethylamino-N-Me acetamide in DMF using N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride as condensing agent. In pharmacol. testing, I had receptor affinity IC50 values of 17.0 nM and 25.0 M using FXa and TF/FVIIa receptors, resp. (no details given). Various formulations for administering the title compds. therapeutically are given.

IT 855855-29-7P

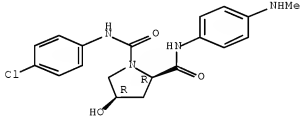
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of prolinylarylacetamides as coagulation factor Xa inhibitors for prevention or treatment of thromboembolic diseases or tumors)

RN 855855-29-7 HCAPLUS

CN 1,2-Pyrrolidinedicarboxamide, N1-(4-chlorophenyl)-4-hydroxy-N2-[4-(methylamino)phenyl]-, (2R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:1124627 HCAPLUS Full-text

DOCUMENT NUMBER: 142:74838

TITLE: Preparation of pyrrolidin-1,2-dicarboxylic acids and related compounds as coagulation factor Xa and factor VIIa inhibitors

INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes

PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany

SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

10551670

LANGUAGE: German
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004110433	A1	20041223	WO 2004-EP5717	20040527
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10327428	A1	20050105	DE 2003-10327428	20030618
DE 10329457	A1	20050120	DE 2003-10329457	20030701
AU 2004246766	A1	20041223	AU 2004-246766	20040527
CA 2529453	A1	20041223	CA 2004-2529453	20040527
EP 1633346	A1	20060315	EP 2004-735007	20040527
EP 1633346	B1	20060823		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
BR 2004011466	A	20060711	BR 2004-11466	20040527
CN 1809346	A	20060726	CN 2004-80016955	20040527
AT 337000	T	20060915	AT 2004-735007	20040527
JP 2006527708	T	20061207	JP 2006-515798	20040527
ES 2271894	T3	20070416	ES 2004-735007	20040527
IN 2005KN02399	A	20070727	IN 2005-KN2399	20051128
MX 2005PA13536	A	20060309	MX 2005-PA13536	20051213
US 20070093472	A1	20070426	US 2005-561227	20051219

PRIORITY APPLN. INFO.:			
	DE 2003-10327428	A	20030618
	DE 2003-10329457	A	20030701
	WO 2004-EP5717	W	20040527

OTHER SOURCE(S): MARPAT 142:74838
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R = H, X, A, etc.; R1 = H, =O, halo, etc.; R2 = H, halo, A; R3 = (un)substituted aromatic heterocycle containing 1-4 N, O, S atoms; X = aryl, arylalkyl, het, etc.; A = (un)substituted cycloalkyl] and their pharmaceutically acceptable salts and formulations were prepared For example, condensation of proline II, e.g., prepared from BOC-methoxyproline in 3-steps, and 4-nitrophenylchloroformate and 4-ethynylaniline afforded claimed pyrrolidinyldicarboxylic III in 40% yield. In coagulation factor Xa receptor affinity binding assays, 14-examples of compds. I exhibited IC50 values ranging from 1.1-4.8 nM, i.e., the IC50 value of pyrrolidinyldicarboxylic III was 1.3 nM. Compds. I are claimed to be useful as factor Xa and factor VIIa inhibitors for the treatment of thromboembolic diseases.

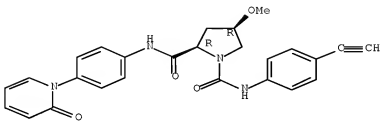
IT 81426?-98-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrrolidinyldicarboxylic acids and related compds. as factor Xa and factor VIIa inhibitors)

RN 814263-98-4 HCAPLUS

CN 1,2-Pyrrolidinedicarboxamide, N1-(4-ethynylphenyl)-4-methoxy-N2-[4-(2-oxo-1(2H)-pyridinyl)phenyl]-, (2R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:857591 HCAPLUS Full-text

DOCUMENT NUMBER: 141:314626

TITLE: Method for the production of pyrrolidine-1,2-dicarboxylic acid-1-(phenyl(-amide))-2-(phenyl(-amide)) derivatives and 1-(phenylcarbamoyl)-pyrrolidine-2-carboxylic acid derivatives as intermediate products

INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes

PATENT ASSIGNEE(S): Merck Patent GmbH, Germany

SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

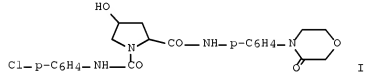
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004087695	A1	20041014	WO 2004-EP2405	20040309
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10315377	A1	20041014	DE 2003-10315377	20030403
DE 10327428	A1	20050105	DE 2003-10327428	20030618
DE 10329295	A1	20050203	DE 2003-10329295	20030630
DE 10329457	A1	20050120	DE 2003-10329457	20030701
DE 10334174	A1	20050217	DE 2003-10334174	20030726

AU 2004226280	A1	20041014	AU 2004-226280		20040309
CA 2520893	A1	20041014	CA 2004-2520893		20040309
EP 1608646	A1	20051228	EP 2004-718646		20040309
EP 1608646	B1	20070711			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK					
BR 2004008888	A	20060411	BR 2004-8888		20040309
JP 2006522037	T	20060928	JP 2006-504602		20040309
EP 1760081	A1	20070307	EP 2006-22891		20040309
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, LT, LV					
US 20060211692	A1	20060921	US 2005-551670		20050930
IN 2005KN02182	A	20060929	IN 2005-KN2182		20051103

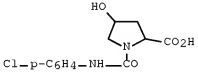
PRIORITY APPLN. INFO.: DE 2003-10315377 A 20030403
DE 2003-10327428 A 20030618
DE 2003-10329295 A 20030630
DE 2003-10329457 A 20030701
DE 2003-10334174 A 20030726
EP 2004-718646 A3 20040309
WO 2004-EP2405 W 20040309

OTHER SOURCE(S): CASREACT 141:314626; MARPAT 141:314626

GI



I



II

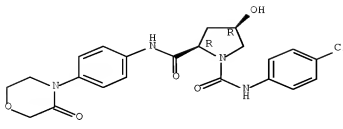
AB The invention relates to a method for the production of title compds., e.g. (I), and intermediate products, e.g. (II) for the production of I. Thus, cis-hydroxy-D-proline was reacted with 4-chlorophenylisocyante in NaHCO3 at 80° for 5 h. to give after workup 81.8% (R,R)-II. II was then reacted with 4-(3-oxo-4-morpholinyl)aniline in THF with 2-ethoxy-1(2H)-quinolinecarboxylic acid Et ester (EEDQ) as coupling agent at room temperature for 20 h to give, after workup, 69% (R,R)-I.

IT 768370-75-8P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of substituted Ph 1,2-pyrrolidinedicarboxylic acid diamides and intermediates)

RN 768370-75-8 HCAPLUS

CN 1,2-Pyrrolidinedicarboxamide, N1-(4-chlorophenyl)-4-hydroxy-N2-[4-(3-oxo-4-morpholinyl)phenyl]-, (2R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:857551 HCAPLUS Full-text
DOCUMENT NUMBER: 141:350179
TITLE: Preparation of azolidinedicarboxamides and related compounds as Factor Xa and Factor VIIa inhibitors
INVENTOR(S): Tsaklakidis, Christos; Dorsch, Dieter; Mederski, Werner; Cezanne, Bertram; Gleitz, Johannes
PATENT ASSIGNEE(S): Merck Patent GmbH, Germany
SOURCE: PCT Int. Appl., 162 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

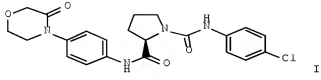
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004087646	A2	20041014	WO 2004-EP2350	20040308
WO 2004087646	A3	20050106		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10315377	A1	20041014	DE 2003-10315377	20030403
DE 10329295	A1	20050203	DE 2003-10329295	20030630
AU 2004226278	A1	20041014	AU 2004-226278	20040308
CA 2521069	A1	20041014	CA 2004-2521069	20040308
BR 2004008420	A	20060321	BR 2004-8420	20040308
JP 2006522033	T	20060928	JP 2006-504581	20040308
EP 1720844	A2	20061115	EP 2004-718299	20040308
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, LT, LV				
IN 2005KN01684	A	20070727	IN 2005-KN1684	20050823
US 20060183739	A1	20060817	US 2005-551557	20051003

PRIORITY APPLN. INFO.: DE 2003-10315377 A 20030403
DE 2003-10329295 A 20030630

US 2003-483897P P 20030702
WO 2004-EP2350 W 20040308

OTHER SOURCE(S): MARPAT 141:350179

GI



I

AB R1R2(TYX)EWCOGD [R1, R2 = H, O, halo, A, ethynyl, OR3, N(R3)2, NO2, cyano, N3, CO2R3, CON(R3)2, etc.; R3 = H, A, HC.tplbond.CCH2, MeC.tplbond.CCH2, CH2CH(OH)CH2OH, etc.; R4 = H, A; W = N, C, CR3; E = atoms to form a 3-7 membered (heterocyclic) ring optionally containing a double bond; D = mono- or dinuclear (substituted) (hetero)aryl; G = [C(R4)2]n, [C(R4)2]nNR3, [C(R4)2]nO, [C(R4)2]nS, etc.; n = 0-2; X = [C(R4)2]nCO[C(R4)2]n, [C(R4)2]n,NR3[C(R4)2]n, [C(R4)2]nNR3CO[C(R4)2]n, etc.; Y = alkylene, cycloalkylene, heterocyclylene, arenediyl; T = substituted mono- or dinuclear carbocyclyl, heterocyclyl; A = (fluoro-substituted) alkyl optionally interrupted by O, S, CH:CH], were prepared Thus, title compound (I) [preparation from 4-(4-aminophenyl)morpholin-3-one, Boc-D-proline, and 4-chlorophenyl isocyanate given] bound to Factor Xa receptors with IC50 = 1.8 + 10-8 M.

IT 536747-22-5P

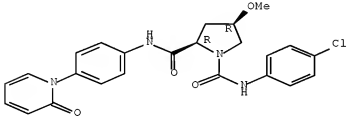
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of azolidinedicarboxamides and related compds. as Factor Xa and Factor VIIa inhibitors)

RN 536747-22-5 HCAPLUS

CN 1,2-Pyrrolidinedicarboxamide, N1-(4-chlorophenyl)-4-methoxy-N2-[4-(2-oxo-1(2H)-pyridinyl)phenyl]-, (2R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:841766 HCAPLUS Full-text

DOCUMENT NUMBER: 141:332202

TITLE: Preparation of azolidinecarboxamides as antithrombotics and anticancer drugs.

INVENTOR(S): Tsaklakidis, Christos; Dorsch, Dieter; Mederski, Werner; Cezanne, Bertram; Gleitz, Johannes

PATENT ASSIGNEE(S): Merck Patent GmbH, Germany

10551670

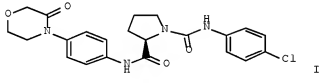
SOURCE: Ger. Offen., 47 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10315377	A1	20041014	DE 2003-10315377	20030403
AU 2004226278	A1	20041014	AU 2004-226278	20040308
CA 2521069	A1	20041014	CA 2004-2521069	20040308
WO 2004087646	A2	20041014	WO 2004-EP2350	20040308
WO 2004087646	A3	20050106		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
BR 2004008420	A	20060321	BR 2004-8420	20040308
CN 1771237	A	20060510	CN 2004-80009354	20040308
JP 2006522033	T	20060928	JP 2006-504581	20040308
EP 1720844	A2	20061115	EP 2004-718299	20040308
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, LT, LV				
AU 2004226280	A1	20041014	AU 2004-226280	20040309
AU 2004226281	A1	20041014	AU 2004-226281	20040309
CA 2520893	A1	20041014	CA 2004-2520893	20040309
CA 2520894	A1	20041014	CA 2004-2520894	20040309
WO 2004087695	A1	20041014	WO 2004-EP2405	20040309
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2004087696	A1	20041014	WO 2004-EP2407	20040309
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1608645	A1	20051228	EP 2004-718641	20040309

EP 1608645	B1	20070502				
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK						
EP 1608646	A1	20051228	EP 2004-718646			20040309
EP 1608646	B1	20070711				
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK						
BR 2004008444	A	20060404	BR 2004-8444			20040309
BR 2004008888	A	20060411	BR 2004-8888			20040309
CN 1771248	A	20060510	CN 2004-80009374			20040309
CN 1771249	A	20060510	CN 2004-80009463			20040309
JP 2006522037	T	20060928	JP 2006-504602			20040309
JP 2006522038	T	20060928	JP 2006-504604			20040309
AT 361296	T	20070515	AT 2004-718641			20040309
AT 366732	T	20070815	AT 2004-718646			20040309
ES 2285444	T3	20071116	ES 2004-718641			20040309
ES 2287708	T3	20071216	ES 2004-718646			20040309
IN 2005KN01684	A	20070727	IN 2005-KN1684			20050823
US 20060211692	A1	20060921	US 2005-551670			20050930
US 20060183739	A1	20060817	US 2005-551557			20051003
US 20060183742	A1	20060817	US 2005-551559			20051003
IN 2005KN02182	A	20060929	IN 2005-KN2182			20051103
IN 2005KN02183	A	20070323	IN 2005-KN2183			20051103
PRIORITY APPLN. INFO.:			DE 2003-10315377	A		20030403
			DE 2003-10327428	A		20030618
			DE 2003-10329295	A		20030630
			DE 2003-10329457	A		20030701
			US 2003-483897P	P		20030702
			DE 2003-10334174	A		20030726
			DE 2003-10336570	A		20030808
			WO 2004-EP2350	W		20040308
			WO 2004-EP2405	W		20040309
			WO 2004-EP2407	W		20040309

OTHER SOURCE(S): MARPAT 141:332202

GI



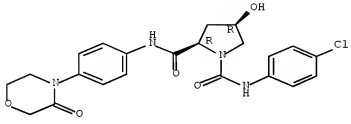
I

AB R1R2(TYX)EWCOGD [R1, R2 = H, O, halo, A, ethynyl, OR3, NO2, cyano, N3, CO2R3, CON(R3)2, NR3COA, NR3SO2A, etc.; R1R2 = toms to form a bicyclic or spirocyclic (heterocyclic) ring; R3 = H, A, etc.; R4 = H, A; W = N, CR3, C; E = atoms to form a 3-7 membered (double bond containing) (heterocyclic) ring with W; G = [C(R4)2]n, [C(R4)2]nNR3, [C(R4)2]nO, [C(R4)2]nS; X = [C(R4)2]nCONR3[C(R4)2]n, [C(R4)2]nON[C(R4)2]n, etc.; Y = alkylene, cycloalkylene, (substituted) heterocyclylene, arylene; T = mono- or bicyclic substituted (unsatd.) (hetero)cyclyl; A = (fluoro-substituted) alkylene optionally interrupted by O, S, CH:CH; n = 0-2], were prepared Thus, title compound (I) (prepared from 4-(4-aminophenyl)morpholin-3-one, Boc-D-proline, and 4-chlorophenyl isocyanate), bound to Factor Xa receptors with IC50 = 1.8 + 10-8 M.

IT 768370-75-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of azolidinecarboxamides as antithrombotics and
anticancer drugs)
RN 768370-75-8 HCAPLUS
CN 1,2-Pyrrolidinedicarboxamide, N1-(4-chlorophenyl)-4-hydroxy-N2-[4-(3-oxo-4-morpholinyl)phenyl]-, (2R,4R)- (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:799558 HCAPLUS Full-text
DOCUMENT NUMBER: 141:296012
TITLE: Preparation of factor Xa- and thrombin-inhibiting substituted benzamidines and sulfonylbenzamidines as potential anticoagulants
INVENTOR(S): Pinto, Donald J.; Qiao, Jennifer X.; Gangor, Timur; Lam, Patrick Y. S.; Li, Yun-long
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 279 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004083174	A2	20040930	WO 2004-US8033	20040317
WO 2004083174	A3	20041125		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20040209863	A1	20041021	US 2004-801518	20040316
US 7122557	B2	20061017		
EP 1603562	A2	20051214	EP 2004-757516	20040317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK

PRIORITY APPLN. INFO.: US 2003-455709P P 20030318
US 2004-801518 A 20040316
WO 2004-US8033 W 20040317

OTHER SOURCE(S): MARPAT 141:296012

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

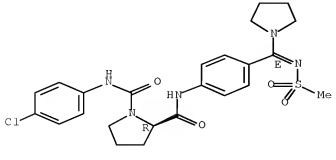
AB Compds. P4-M-M4 (I) [M = (un)substituted 3-10 membered carbocyclic or a 4-10 membered heterocyclic ring containing 1-3 O, N, or S atoms, alone or fused to an (un)substituted 5-7 membered carbocycle or heterocycle; P4 = Z-A-B; M4 = G-G1; A = (un)substituted 3-10 membered carbocyclic or 5-12 membered heterocyclic ring ; B = (un)substituted amidino, guanidino, iminomethyl; G = five or six-membered carbocycle or heterocycle fused to a benzene, pyridine, pyrimidine, pyrazine, or pyridazine ring; G1 = bond, (un)substituted alkyl, alkenyl, alkynyl; Z = (un)substituted alkylene], such as tetrahydropyrazolo[3,4-c]pyridinone II or (pyridinylaminocarbonylphenylaminocarbonyl)benzamidine III are prepared as inhibitors of Factor Xa and thrombin for use as anticoagulants. Deprotonation of 2-amino-4-chloropyridine and addition to 5-chloroisatoic anhydride yields N-(5-chloro-2-pyridinyl) 2-amino-5-chlorobenzamide (IV). Acid-mediated addition of dimethylamine to the nitrile of Me 4-cyanobenzoate, mesylation of the amidine nitrogen, and base-mediated hydrolysis of the ester yields 4-(N,N-dimethyl-N'-methylsulfonylamidino)benzoic acid (V). Coupling of IV and V mediated by BOP yields III. Some compds. of the invention inhibit human factor Xa with Ki values of ≤ 10 μM; in addition, some of the invention compds. inhibit thrombin in vitro. (no data).

IT 764658-81-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of factor Xa- and thrombin-inhibiting substituted benzamidines and sulfonylbenzamidines as potential anticoagulants)

RN 764658-81-3 HCAPLUS

CN 1,2-Pyrrolidinedicarboxamide, N1-(4-chlorophenyl)-N2-[4-[(E)-[(methylsulfonyl)imino]-1-pyrrolidinylmethyl]phenyl]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



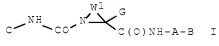
L6 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:434528 HCAPLUS Full-text
DOCUMENT NUMBER: 139:6763
TITLE: Preparation of pyrrolidinedicarboxamides and related compounds as inhibitors of factor Xa useful for thrombotic disorders
INVENTOR(S): Bigge, Christopher Franklin; Dudley, Danette Andrea; Edmunds, Jeremy John; Van Huis, Chad Alan; Casimiro-Garcia, Agustin; Filipski, Kevin James; Kohrt, Jeffrey Thomas
PATENT ASSIGNEE(S): Warner-Lambert Company L.L.C., USA
SOURCE: PCT Int. Appl., 389 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003045912	A1	20030605	WO 2002-IB4757	20021114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20030162787	A1	20030828	US 2002-278643	20021023
US 7030141	B2	20060418		
CA 2468715	A1	20030605	CA 2002-2468715	20021114
AU 2002365313	A1	20030610	AU 2002-365313	20021114
AU 2002365313	B2	20080306		
BR 2002014519	A	20041013	BR 2002-14519	20021114
EP 1465864	A1	20041013	EP 2002-803885	20021114
EP 1465864	B1	20060315		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
CN 1582274	A	20050216	CN 2002-823837	20021114
HU 2004002529	A2	20050329	HU 2004-2529	20021114
JP 2005515985	T	20050602	JP 2003-547364	20021114
AT 320414	T	20060415	AT 2002-803885	20021114
EP 1671949	A2	20060621	EP 2006-110738	20021114
EP 1671949	A3	20060719		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
PT 1465864	T	20060630	PT 2002-803885	20021114
ES 2259113	T3	20060916	ES 2002-803885	20021114
NZ 532384	A	20061027	NZ 2002-532384	20021114
AP 1744	A	20070630	AP 2004-3035	20021114
MX 2004PA03606	A	20040727	MX 2004-PA3606	20040416
ZA 2004004085	A	20050905	ZA 2004-4085	20040525
NO 2004002270	A	20040601	NO 2004-2270	20040601
US 20050267118	A1	20051201	US 2004-17598	20041220
US 20050250815	A1	20051110	US 2005-108582	20050418
US 20060264626	A1	20061123	US 2006-461859	20060802
PRIORITY APPLN. INFO.:			US 2001-334168P P	20011129

US 2002-384895P	P	20020531
US 2002-278643	A3	20021023
EP 2002-803885	A3	20021114
WO 2002-IB33416	A	20021114
WO 2002-IB4757	W	20021114
US 2004-17598	A3	20041220

OTHER SOURCE(S): MARPAT 139:6763

GI



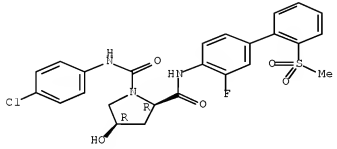
I

AB The present invention provides pyrrolidinedicarboxamides and related compds. (shown as I; variables defined below; e.g. (R)-pyrrolidine-1,2- dicarboxylic acid 1-[(4-chlorophenyl)amide] 2-[(3-fluoro-2'- sulfamoylbiphenyl-4-yl)amide]) and pharmaceutically acceptable salt thereof, that are useful to treat thrombotic disorders. Also disclosed are pharmaceutical compns. comprising ≥1 compds. I, processes for preparing I, and intermediates useful for preparing I. IC50 values for inhibition of factor Xa are tabulated for >170 examples of I. About 180 example prepns. of I are included. For example, (R)-pyrrolidine-1,2- dicarboxylic acid 1-[(4-chlorophenyl)amide] 2-[(3-fluoro-2'-sulfamoylbiphenyl-4-yl)amide] was prepared in 4 steps starting from Fmoc-D-Pro, SOCl2, and 4-bromo-2-fluoroaniline and involving intermediates (R)-2-[(4-bromo-2-fluorophenyl)carbamoyl]pyrrolidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester, (R)-pyrrolidine-2-carboxylic acid (2'-tert-butylsulfamoyl-3-fluorobiphenyl-4-yl)amide, and (R)-pyrrolidine-1,2-dicarboxylic acid 2-[(2'-tert-butylsulfamoyl-3- fluorobiphenyl-4-yl)amide] 1-[(4-chlorophenyl)amide] with yields of 99, 70, 66 and 76%, resp. Four pharmaceutical formulations are described. For I: A is (un)substituted aryl or (un)substituted monocyclic heteroaryl; B is -NHC(O)(C1-C6)alkyl, -NHC(O)(C3-C7)cycloalkyl, -NHC(O)O(C1-C6 alkyl), -C(O)R1, (C3-C7)cycloalkyl, (C3-C7)heterocyclo, (C4-C7)cycloalkenyl, unsatd. (C4-C7)heterocyclo, aryl, or heteroaryl, any of which may be (un)substituted by halo, (C1-C6)alkyl, or halo(C1-C6)alkyl, O(C1-C6), -CN, haloalkyl, amino, alkylamino, amidino, amido, or sulfonamido. C is Ph or heteroaryl, wherein Ph or heteroaryl is (un)substituted with ≥1 substituents = aryl, heteroaryl, halogen, hydroxy, -CO2R2, -COR2, -CONR2R2', alkoxy, alkyl, -CN, haloalkyl, amino, alkylamino, amidino, amido, or sulfonamido; G is H, halo, (C1-C6)alkyl, halo(C1-C6)alkyl, hydroxy(C1-C6)alkyl, -CH2O(C1-C6)alkyl, -CH2CO2(C1-C6)alkyl, -CH2NR2R2', or -CH2C(O)NH(C1-C6)alkyl. W1 is a saturated or unsatd., (un)substituted hydrocarbon chain or hydrocarbon-heteroatom chain having 2-6 atoms, wherein W1 connects the N atom at position 1 to the C atom at position 2 to form a four to eight membered ring; R1 is (C1-C6)alkoxy, (C3-C7)cycloalkyl, (C3-C7)heterocycloalkyl, (C4-C7) cycloalkenyl, (C4-C7)heterocycloalkenyl, aryl, monocyclic heteroaryl, or -NR3R4; R2 and R2' are each independently H or (C1-C6)alkyl; and R3 and R4 are each independently H, (C1-C6)alkyl, aralkyl, aryl, monocyclic heteroaryl, alkoxycarbonyl, aralkoxycarbonyl, -SO2alkyl, or joined together to form a saturated or unsatd. 3 to 7 membered ring.

IT 536746-63-1P, (2R,4R)-4-Hydroxypyrrolidine-1,2-dicarboxylic acid 1-[(4-chlorophenyl)amide] 2-[(3-fluoro-2'-methanesulfonylbiphenyl-4-yl)amide]
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(drug candidate; preparation of pyrrolidinedicarboxamides and related compds. as inhibitors of factor Xa useful for thrombotic disorders)
RN 536746-63-1 HCAPLUS
CN 1,2-Pyrrolidinedicarboxamide, N1-(4-chlorophenyl)-N2-[3-fluoro-2'-(methylsulfonyl)[1,1'-biphenyl]-4-yl]-4-hydroxy-, (2R,4R)- (CA INDEX NAME)

Absolute stereochemistry.

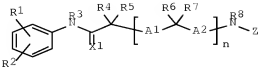


REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:352811 HCAPLUS Full-text
DOCUMENT NUMBER: 129:40984
ORIGINAL REFERENCE NO.: 129:8615a,8618a
TITLE: Preparation of acylamino-substituted acylanilide derivatives as antiandrogenic agents
INVENTOR(S): Taniguchi, Nobuaki; Okada, Minoru; Kaku, Hidetaka; Shimada, Itsuro; Nozawa, Eisuke; Koutoku, Hiroshi; et al.
PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9822432	A1	19980528	WO 1997-JP4174	19971117
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9749664	A	19980610	AU 1997-49664	19971117
PRIORITY APPLN. INFO.:			JP 1996-306192 A	19961118
			WO 1997-JP4174 W	19971117

OTHER SOURCE(S): MARPAT 129:40984
GI



I

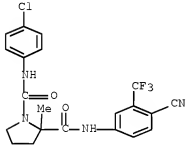
AB The title compds. [I; R1, R2 = halo, cyano, haloalkyl, NO2, etc.; R3 = H, lower alkyl; R4-R7 = H, (un)substituted lower alkyl, aralkyl, etc.; R8 = H, OH, lower alkoxy or alkyl, etc.; n = 0, 1; A1, A2 = lower alkylene; Z = acyl; X1 = O, S] are prepared I have an antiandrogenic activity and are useful as a prophylactic or therapeutic agent for prostatic cancer, prostatic hypertrophy, defemination, hypertrichosis, bald head, acne, seborrhea and the like in which androgen is involved as an exacerbating factor. Thus, p-FC6H4SO2NHCHEtCO2H was treated with (COCl)2 and then reacted with 4-amino-2-trifluoromethylbenzonitrile to give I (R1 = CF3, R2 = cyano, R3 = R5 = R8 = H, n = 0, Z = p-FC6H4SO2, X1 = O), which showed IC50 of 0.56 nM antagonist activity when tested with androgen receptor.

IT 208121-51-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of acylamino-substituted acylanilide derivs. as antiandrogenic agents)

RN 208121-51-1 HCAPLUS

CN 1,2-Pyrrolidinedicarboxamide, N1-(4-chlorophenyl)-N2-[4-cyano-3-(trifluoromethyl)phenyl]-2-methyl- (CA INDEX NAME)



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> fil reg

FILE 'REGISTRY' ENTERED AT 15:40:22 ON 18 JUN 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 17 JUN 2008 HIGHEST RN 1028750-52-8
DICTIONARY FILE UPDATES: 17 JUN 2008 HIGHEST RN 1028750-52-8

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 9, 2008.

Please note that search-term pricing does apply when conducting SmartSELECT searches.

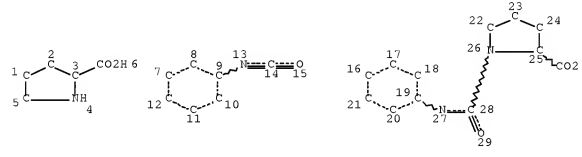
REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> => dis his l13-

(FILE 'CASREACT' ENTERED AT 15:41:29 ON 18 JUN 2008)
L13 5 S L11 FUL

=> d l13 que stat;d 1-5 ibib abs fhit
L11 STR



Page 1-A

H 30

Page 1-B
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 30

STEREO ATTRIBUTES: NONE
L13 5 SEA FILE=CASREACT SSS FUL L11 (10 REACTIONS)

100.0% DONE 117 VERIFIED 10 HIT RXNS 5 DOCS
SEARCH TIME: 00.00.01

L13 ANSWER 1 OF 5 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 143:7713 CASREACT Full-text
TITLE: Preparation of spiro-heterocyclic compounds for treating inflammatory diseases and immune diseases
INVENTOR(S): Dhar, T. G. Murali; Iwanowicz, Edwin; Launay, Michele; Potin, Dominique; Blandine, Maillet Magali Jeannine; Nicolai, Eric
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA; Cerep SA
SOURCE: U.S. Pat. Appl. Publ., 27 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

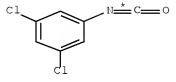
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050119279	A1	20050602	US 2004-957255	20041001
US 7199125	B2	20070403		
PRIORITY APPLN. INFO.:			US 2003-508165P	20031002

OTHER SOURCE(S): MARPAT 143:7713
GI

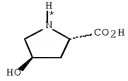
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention is directed to compds. having the formula (I) [K, L = O, S; Q = a bond, CO, (un)substituted branched or straight chain C1-6 alkylene; Ar = aryl, heteroaryl; Y = a bond, (un)substituted CH2; J1, J2, J3 = each (un)substituted NH or CH2; provided that only one of J1, J2, and J3 may be (un)substituted NH, so that ring A is a five- to six- membered cycloalkyl or heterocycle ring having from 0 to 2 heteroatoms; R1 = N, (un)substituted CH; R2, R3 = H, halo, NO2, cyano, (un)substituted alkyl or alkenyl, SR12, OR12, NR12R13, CO2R12, COR12, CONR12R13, aryl, heterocyclyl, cycloalkyl, heteroaryl; wherein R12, R13 = hydrogen, (un)substituted alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl; or R12 and R13 when attached to the same nitrogen atom may be taken together to form a heteroaryl or heterocyclyl ring], stereoisomers, pharmaceutically acceptable salts, or hydrates, or prodrug thereof. These compds. are inhibitors of leukointegrins [integrins CD11/CD18, namely lymphocyte function-associated antigen 1 (LFA-1) and macrophage antigen 1 (Mac-1)] and intercellular adhesion mols. (ICAMs such as ICAM-1, ICAM-2, and ICAM-3) (no data). They are useful for treating LFA-1/ICAM-associated conditions, in particular inflammatory and immune diseases. Thus, to a solution of (7aS)-7a-[(4-bromophenyl)methyl]-2-(3,5-dichlorophenyl)dihydro-1H-pyrrolo[1,2-c]imidazole-1,3,6(2H,5H)-trione (0.12 g, 0.26 mmol) and (S)-lactamide (0.114 g, 1.3 mmol) in xylene (20 mL) was added p-toluenesulfonic acid (10 mg) and the resulting mixture was refluxed with the azeotropic removal of water for 18 h to give, after workup and silica gel chromatog., 1'H,4H-spiro(1,3-oxazolidine-2,6'-pyrrolo[1,2-c]imidazole)- 1',3',4(2'H)-trione (II) and (III).

RX(5) OF 97 M + Q ===> R...

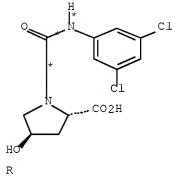


M



Q

(5)



R

RX(5) RCT M 34893-92-0, Q 51-35-4
RGT O 584-08-7 K2CO3
PRO R 433289-45-3
SOL 7732-18-5 Water, 109-99-9 THF
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) overnight, room temperature
NTE incremental addition of the reagent
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

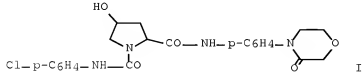
L13 ANSWER 2 OF 5 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 141:314626 CASREACT Full-text
TITLE: Method for the production of pyrrolidine-1,2-dicarboxylic acid-1-(phenyl(-amide))-2-(phenyl(-amide)) derivatives and 1-(phenylcarbamoyl)-pyrrolidine-2-carboxylic acid derivatives as intermediate products
INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes
PATENT ASSIGNEE(S): Merck Patent GmbH, Germany
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

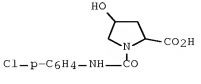
WO 2004087695	A1	20041014	WO 2004-EP2405	20040309
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10315377	A1	20041014	DE 2003-10315377	20030403
DE 10327428	A1	20050105	DE 2003-10327428	20030618
DE 10329295	A1	20050203	DE 2003-10329295	20030630
DE 10329457	A1	20050120	DE 2003-10329457	20030701
DE 10334174	A1	20050217	DE 2003-10334174	20030726
AU 2004226280	A1	20041014	AU 2004-226280	20040309
CA 2520893	A1	20041014	CA 2004-2520893	20040309
EP 1608646	A1	20051228	EP 2004-718646	20040309
EP 1608646	B1	20070711		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
BR 2004008888	A	20060411	BR 2004-8888	20040309
JP 2006522037	T	20060928	JP 2006-504602	20040309
EP 1760081	A1	20070307	EP 2006-22891	20040309
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, LT, LV				
US 20060211692	A1	20060921	US 2005-551670	20050930
IN 2005KN02182	A	20060929	IN 2005-KN2182	20051103
PRIORITY APPLN. INFO.:			DE 2003-10315377	20030403
			DE 2003-10327428	20030618
			DE 2003-10329295	20030630
			DE 2003-10329457	20030701
			DE 2003-10334174	20030726
			EP 2004-718646	20040309
			WO 2004-EP2405	20040309

OTHER SOURCE(S): MARPAT 141:314626

GI



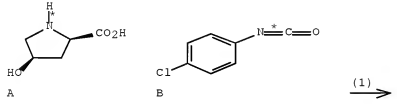
I



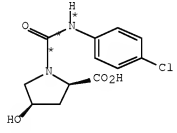
II

AB The invention relates to a method for the production of title compds., e.g. (I), and intermediate products, e.g. (II) for the production of I. Thus, cis-hydroxy-D-proline was reacted with 4-chlorophenylisocyante in NaHCO3 at 80° for 5 h. to give after workup 81.8% (R,R)-II. II was then reacted with 4-(3-oxo-4-morpholinyl)aniline in THF with 2-ethoxy-1(2H)-quinolinecarboxylic acid Et ester (EEDQ) as coupling agent at room temperature for 20 h to give, after workup, 69% (R,R)-I.

RX(1) OF 4 A + B ===> C...



A B (1)



C
YIELD 82%

RX(1) RCT A 2584-71-6, B 104-12-1

STAGE(1)
RGT D 144-55-8 NaHCO3
SOL 7732-18-5 Water
CON SUBSTAGE(1) 5 hours, 80 deg C
SUBSTAGE(2) 80 deg C -> room temperature

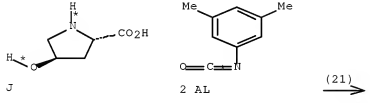
STAGE(2)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water
CON room temperature, pH 1

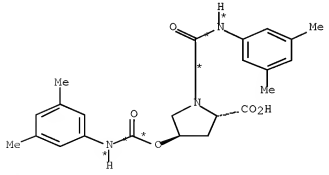
PRO C 768379-72-5
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 5 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 141:207487 CASREACT Full-text
TITLE: Synthetic studies on L-proline and (4R)-hydroxy-L-proline derivatives
AUTHOR(S): Gonzalez, Teresa; Abad, Olga; Santano, M. Carmen; Minguillon, Cristina
CORPORATE SOURCE: Laboratori de Quimica Farmaceutica, Facultat de Farmacia, Universitat de Barcelona, Barcelona, 08028, Spain
SOURCE: Synthesis (2004), (8), 1171-1182
CODEN: SYNTBF; ISSN: 0039-7881
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The preparation of a number of L-proline and (4R)-hydroxy-L-proline derivs. to assess their enantioselectivity when applied to several techniques and exptl. conditions is described. All the derivs. prepared via acylation of amino group in amino acid, followed by the reaction with appropriate amines incorporated at least one 3,5-disubstituted aromatic ring that contained nitro, chloro or Me groups and were obtained by classical methods. In spite of the difficulties that arise from the presence of rotational isomers in most cases, the compds. studied are fully described by their 1H and 13C NMR spectra.

RX(21) OF 75 J + 2 AL ===> AM





YIELD 78%

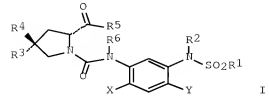
RX(21) RCT J 51-35-4, AL 54132-75-1

RGT AN 110-86-1 Pyridine
PRO AM 744253-81-4
CON 5 hours, reflux
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 5 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 129:202944 CASREACT Full-text
TITLE: Preparation of intermediates and 1,3-dioxo-1H-pyrrolo[1,2-c]imidazoles
INVENTOR(S): Taylor, Eric Deguyon; Petrov, Viacheslav Alexandrovich; Schaefer, Matthias; Drauz, Karlheinz; Vogt, Anne; Weckbecker, Christoph; Swearingen, Steven H.; Kamireddy, Balreddy
PATENT ASSIGNEE(S): E. I. Du Pont de Nemours & Co., USA; Degussa A.-G.
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9837065	A1	19980827	WO 1998-US2721	19980213
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
IN 1998CA00208	A	20051118	IN 1998-CA208	19980209
ZA 9801168	A	19990812	ZA 1998-1168	19980212
CA 2276056	A1	19980827	CA 1998-2276056	19980213
AU 9861604	A	19980909	AU 1998-61604	19980213
EP 973739	A1	20000126	EP 1998-906363	19980213
EP 973739	B1	20051102		
R: DE, FR, IT				
BR 9807256	A	20000502	BR 1998-7256	19980213
US 6384234	B1	20020507	US 1999-367899	19991230
US 20020137946	A1	20020926	US 2002-35136	20020104
US 6664400	B2	20031216		
PRIORITY APPLN. INFO.:			US 1997-38429P	19970219
			WO 1998-US2721	19980213
			US 1999-367899	19991230
OTHER SOURCE(S):		MARPAT 129:202944		

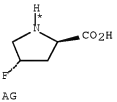
GI



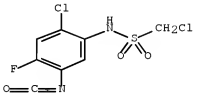
I

AB Title compds. [I; R1 = haloalkyl, alkoxyalkyl, cyanoalkyl, etc.; R2 = H, (halo)alkyl, alkanoyl, alkoxycarbonyl, etc.; R3 = H or OH; R4,X = H, F, Cl; Y = F or Cl; R5 = OH; R6 = H; R5R6 = bond] were prepared Thus, N-(2-chloro-4-fluoro-5-isocyanatophenyl)chloromethanesulfonamide (preparation given) was amidated by cis-4-hydroxy-D-proline to give I (R1 = Y = Cl, R2 = H, X = F)(II; R4 = R6 = H, R3 = R5 = OH) which was cyclized and the product fluorinated to give II (R3 = H, R4 = F, R5R6 = bond).

RX(11) OF 34 ...AG + AJ ===> AK

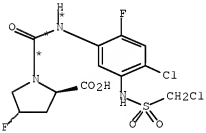


AG



AJ

(11)



AK

RX(11) RCT AG 131176-02-8, AJ 212198-49-7

STAGE(1)
SOL 109-99-9 THF

STAGE(2)
RGT AC 144-55-8 NaHCO3
SOL 7732-18-5 Water, 141-78-6 AcOEt

STAGE(3)
RGT I 7647-01-0 HCl
SOL 7732-18-5 Water, 109-99-9 THF

PRO AK 212198-50-0

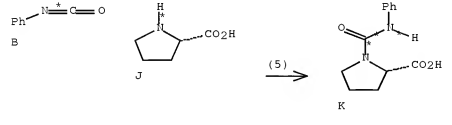
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 5 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 115:29919 CASREACT Full-text
TITLE: Process for preparation of unsymmetrical ureas and thioureas
INVENTOR(S): Henklein, Peter; Boettcher, Mathias; Georgi, Monika; Heder, Gottfried; Siems, Wolf Eberhard; Niedrich, Hartmut
PATENT ASSIGNEE(S): Akademie der Wissenschaften der DDR, Germany
SOURCE: Ger. (East), 3 pp.
CODEN: GEXXA8
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DD 285975	A5	19910110	DD 1985-294362	19851223

PRIORITY APPLN. INFO.: DD 1985-294362 19851223
OTHER SOURCE(S): MARPAT 115:29919
AB A process for the preparation of ureas R1NHCOR2 (R1 = aryl, alkyl; R2 = amino acid group, amino acid ester group) or thioureas R1NHCSR2 (same R1, R2) comprises the silylation of amino acid tosylates and subsequent treatment of the products with isocyanate or isothiocyanate. The sequential treatment of amino acid ester hydrochlorides with COCl2 and amino acid esters gives R1NHCOR2 (same R1, R2). Unsym. ureas or thioureas are potential inhibitors for angiotensin-converting enzyme which represents an approach to the treatment of renal hypertension. Isoleucine tosylate was silylated with hexamethyldisilazane and treated with PhNCO to give PhNHCONH(CO2H)CHMeEt (I). The IC50 of I for in vitro inhibition of angiotensin-converting enzyme was 70 μM. The IC50 of PhNHC(:S)NH(CO2H)CHMeEt was 165 μM.

RX(5) OF 6 B + J ===> K



RX(5) RCT B 103-71-9, J 147-85-3
PRO K 73696-22-7

=> fil medl,biosis,embase,hcaplus;s mederski w?/au;s tsaklakidis c?/au;s dorsch d?/au;s cezanne b?/au;s gleitz j?/au

FILE 'MEDLINE' ENTERED AT 15:45:51 ON 18 JUN 2008

```
FILE 'BIOSIS' ENTERED AT 15:45:51 ON 18 JUN 2008
Copyright (c) 2008 The Thomson Corporation

FILE 'EMBASE' ENTERED AT 15:45:51 ON 18 JUN 2008
Copyright (c) 2008 Elsevier B.V. All rights reserved.

FILE 'HCAPLUS' ENTERED AT 15:45:51 ON 18 JUN 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)


L14           9 FILE MEDLINE
L15          43 FILE BIOSIS
L16          21 FILE EMBASE
L17         144 FILE HCAPLUS

TOTAL FOR ALL FILES
L18         217 MEDERSKI W?/AU


L19           2 FILE MEDLINE
L20          17 FILE BIOSIS
L21           2 FILE EMBASE
L22          78 FILE HCAPLUS

TOTAL FOR ALL FILES
L23          99 TSAKLAKIDIS C?/AU


L24          11 FILE MEDLINE
L25          47 FILE BIOSIS
L26          16 FILE EMBASE
L27         185 FILE HCAPLUS

TOTAL FOR ALL FILES
L28         259 DORSCH D?/AU


L29           4 FILE MEDLINE
L30          10 FILE BIOSIS
L31           4 FILE EMBASE
L32          48 FILE HCAPLUS

TOTAL FOR ALL FILES
L33          66 CEZANNE B?/AU


L34          26 FILE MEDLINE
L35          39 FILE BIOSIS
L36          31 FILE EMBASE
L37          83 FILE HCAPLUS

TOTAL FOR ALL FILES
L38         179 GLEITZ J?/AU

=> s l18 and l23 and l28 and l33 and l38
L39           2 FILE MEDLINE
L40           6 FILE BIOSIS
```

```
L41           2 FILE EMBASE
L42          34 FILE HCAPLUS

TOTAL FOR ALL FILES
L43          44 L18 AND L23 AND L28 AND L33 AND L38

=> dup rem l43
PROCESSING COMPLETED FOR L43
L44          38 DUP REM L43 (6 DUPLICATES REMOVED)

=> d 1-38 ibib abs

L44  ANSWER 1 OF 38  BIOSIS  COPYRIGHT (c) 2008 The Thomson Corporation  on STN
ACCESSION NUMBER:    2008:250260  BIOSIS  Full-text
DOCUMENT NUMBER:     PREV200800265066
TITLE:               Phenyl derivatives.
AUTHOR(S):           Anonymous; Dorsch, Dieter [Inventor];
                     Mederski, Werner [Inventor]; Tsakiakidis,
                     Christos [Inventor]; Cezanne, Bertram
                     [Inventor]; Gleitz, Johannes [Inventor]; Barnes,
                     Christopher [Inventor]
CORPORATE SOURCE:    Ober Ramstadt, Germany
                     ASSIGNEE: Merck Patent GmbH
PATENT INFORMATION:  US 07273867 20070925
SOURCE:              Official Gazette of the United States Patent and Trademark
                     Office Patents, (SEP 25 2007)
                     CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE:       Patent
LANGUAGE:            English
ENTRY DATE:          Entered STN: 9 Apr 2008
                     Last Updated on STN: 9 Apr 2008
AB   Novel compounds of the formula I in which W, X, Y, T, R(1 )and R(2 )are as
     defined in Patent claim 1, are inhibitors of coagulation factor Xa and can be
     employed for the prophylaxis and/or therapy of thromboembolic disorders


L44  ANSWER 2 OF 38  BIOSIS  COPYRIGHT (c) 2008 The Thomson Corporation  on STN
ACCESSION NUMBER:    2007:280692  BIOSIS  Full-text
DOCUMENT NUMBER:     PREV200700267680
TITLE:               Derivatives of phenoxy-n-' 4-(isothiazolindin-1,
                     1-dioxid-2yl)phenyll-valerian-acid amide and other
                     compounds as inhibitors of the coagulation factor xa in the
                     treatment of thromboembolic diseases and tumors.
AUTHOR(S):           Anonymous; Dorsch, Dieter [Inventor];
                     Cezanne, Bertram [Inventor]; Tsakiakidis,
                     Christos [Inventor]; Mederski, Werner
                     [Inventor]; Gleitz, Johannes [Inventor]; Barnes,
                     Christopher [Inventor]
CORPORATE SOURCE:    Ober Ramstadt, Germany
                     ASSIGNEE: Merck Patent Gesellschaft
PATENT INFORMATION:  US 07199133 20070403
SOURCE:              Official Gazette of the United States Patent and Trademark
                     Office Patents, (APR 3 2007)
                     CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE:       Patent
LANGUAGE:            English
ENTRY DATE:          Entered STN: 25 Apr 2007
                     Last Updated on STN: 25 Apr 2007
AB   Novel compounds of formula (I), wherein D, W, X, Y, T and R(1 )have the
     meanings cited in claim 1, are inhibitors of coagulation factor Xa and can be
```

used for the prophylaxis and/or therapy of thromboembolic diseases and in the treatment of tumors

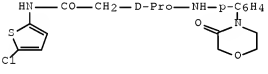
L44 ANSWER 3 OF 38 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2007:194788 BIOSIS Full-text
DOCUMENT NUMBER: PREV200700192695
TITLE: Carboxylic acid amides.
AUTHOR(S): Anonymous; Dorsch, Dieter [Inventor]; Mederski, Werner [Inventor]; Gleitz, Johannes [Inventor]; Cezanne, Bertram [Inventor]; Tsaklakidis, Christos [Inventor]; Barnes, Christopher [Inventor]
CORPORATE SOURCE: Ober Ramstadt, Germany
ASSIGNEE: Merck Patent GmbH
PATENT INFORMATION: US 07183277 20070227
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (FEB 27 2007)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Mar 2007
Last Updated on STN: 14 Mar 2007
AB Novel compounds of the formula I in which D, W, X, Y, T and R(1)are as defined in Patent Claim 1, are inhibitors of coagulation factor Xa and can be employed for the prophylaxis and/or therapy of thromboembolic diseases and for the treatment of tumours.

L44 ANSWER 4 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:318582 HCAPLUS Full-text
DOCUMENT NUMBER: 144:350972
TITLE: Proline derivatives
INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006034789	A1	20060406	WO 2005-EP10025	20050916
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
DE 102004047255	A1	20060413	DE 2004-102004047255	20040929

AU 2005289184	A1	20060406	AU 2005-289184		20050916
CA 2581737	A1	20060406	CA 2005-2581737		20050916
EP 1797079	A1	20070620	EP 2005-787227		20050916
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR					
CN 101031566	A	20070905	CN 2005-80032791		20050916
JP 2008514656	T	20080508	JP 2007-533902		20050916
MX 200703472	A	20070510	MX 2007-3472		20070323
KR 2007058543	A	20070608	KR 2007-707056		20070328
US 20070265259	A1	20071115	US 2007-576226		20070328
IN 2007KN01475	A	20070720	IN 2007-KN1475		20070425
PRIORITY APPLN. INFO.:			DE 2004-102004047255A		20040929
			WO 2005-EP10025	W	20050916

OTHER SOURCE(S): MARPAT 144:350972
GI



I

AB The invention relates to title compds., e.g. (I), which are claimed as inhibitors of the coagulation factor Xa and can be used for the prophylaxis and/or therapy of thromboembolic diseases and for the treatment of tumors (no data). Thus, 4-(4-aminophenyl)morpholin-3-one (II) was condensed with Boc-D-Pro-OH; the resulting intermediate was then coupled with 2-chloro-N-(5-chlorothiophen-2-yl)acetamide to give I. Schemes depicting synthesis of several alternate II starting materials are given (no data), and thirteen alternate I compds. are claimed; formulations for use as injectable forms, suppositories, salves, tablets, dragees, capsules, or ampuls are given.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 5 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:316811 HCAPLUS Full-text
DOCUMENT NUMBER: 144:370085
TITLE: Preparation of 1,2-pyrrolidinedicarboxamides as coagulation factor Xa inhibitors
INVENTOR(S): Cezanne, Bertram; Dorsch, Dieter; Mederski, Werner; Tsaklakidis, Christos; Gleitz, Johannes
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006034769	A1	20060406	WO 2005-EP9418	20050901
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ,				

LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

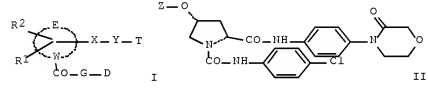
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

DE	102004047254	A1	20060413	DE 2004-102004047254	20040929
AU	2005289164	A1	20060406	AU 2005-289164	20050901
CA	2581732	A1	20060406	CA 2005-2581732	20050901
EP	1797071	A1	20070620	EP 2005-790356	20050901
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
CN	101031561	A	20070905	CN 2005-80032789	20050901
JP	2008514655	T	20080508	JP 2007-533891	20050901
MX	20070347O	A	20070510	MX 2007-3470	20070323
KR	2007057878	A	20070607	KR 2007-707053	20070328
US	20080081814	A1	20080403	US 2007-576207	20070328
IN	2007KN01474	A	20070720	IN 2007-KN1474	20070425

PRIORITY APPLN. INFO.: DE 2004-102004047254A 20040929
WO 2005-EP9418 W 20050901

OTHER SOURCE(S): MARPAT 144:370085

GI



AB Title compds. I [R1, R2 = H, =O, halo, etc.; R3 = H, CH2CH(OH)CH2OH, CH2CH(OH)CH2NH2, etc.; W = N, CR3 with provisos, etc.; E = together with W form a 3 to 7-membered hetero or carbocyclic ring with provisos; D = bond, double bond, etc.; G = [C(R4)2]n, [C(R4)2]nNR3, [C(R4)2]nO, etc.; R4 = H, A; A =alkyl with provisos; X = [C(R4)2]nCONR3[C(R4)2]n, etc.; n = 0-2; Y = alkylene, cycloalkylene, etc.; T = bond, double bond, heterocycle with provisos, etc.] and their pharmaceutically acceptable salts and formulations were prepared For example, O-acylation of hydroxypyrrolidine II [Z = H] afforded pyrrolidinedicarboxamide II [Z = CO2Et]. In coagulation factor Xa inhibition assays, pyrrolidinedicarboxamide II [Z = CO2Et] exhibited an IC50 value of 2.0x10-9 M.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

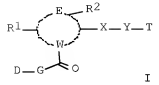
L44 ANSWER 6 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:273940 HCAPLUS Full-text
DOCUMENT NUMBER: 144:331461
TITLE: Drugs containing carbonyl compounds and their use for the prophylaxis and/or therapy of thromboembolic illnesses
INVENTOR(S): Cezanne, Bertram; Dorsch, Dieter; Mederski, Werner; Tsaklakidis,

Christos; Gleitz, Johannes

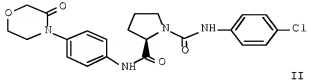
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 77 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 102004045796	A1	20060323	DE 2004-102004045796	20040922
AU 2005287637	A1	20060330	AU 2005-287637	20050824
CA 2581172	A1	20060330	CA 2005-2581172	20050824
WO 2006032342	A2	20060330	WO 2005-EP9124	20050824
WO 2006032342	A3	20070111		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
EP 1791597	A2	20070606	EP 2005-774750	20050824
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
CN 101102818	A	20080109	CN 2005-80031723	20050824
JP 2008513387	T	20080501	JP 2007-531628	20050824
MX 200703175	A	20070518	MX 2007-3175	20070316
KR 2007054210	A	20070528	KR 2007-706440	20070321
US 20080003214	A1	20080103	US 2007-575711	20070321
IN 2007KN01362	A	20070720	IN 2007-KN1362	20070418
PRIORITY APPLN. INFO.:			DE 2004-102004045796A	20040922
			WO 2005-EP9124 W	20050824

OTHER SOURCE(S): MARPAT 144:331461
GI



I



II

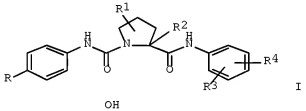
AB Use of heterocyclic carbonyl compds. I [R1, R2 = H, :O,,halogen, A, C.tplbond.CH, OR3,N(R3)2, NO2, CN, N3, CO2R3, CON(R3)2, [C(R4)2]n-Ar, [C(R4)2]n-heterocyclyl, [C(R4)2]n-cycloalkyl, OC(:O)R3, OC(:O)N(R3)2, NR3COA, NR3SO2A; R1R2 = bi- or spirocyclic 3- to 7-membered carbocycle or heterocycle (containing 0 - 3 N, O, or S); R3 = H, A, CH2C.tplbond.CH, CH2CH(OH)CH2OH, CH2CH(OH)CH2NH2, CH2CH(OH)CH2-heterocycle, [C(R4)2]n-Ar, [C(R4)2]n-heterocyclyl, [C(R4)2]n-cycloalkyl, [C(R4)2]n-CO2A, [C(R4)2]nN(R4)2; R4 = H, A; EW = 3- to 7-membered carbocycle or heterocycle (containing 0 - 3 N, O, or S); W = N, CR3, sp2-C; D = mono- or binuclear, (un)substituted aromatic carbocycle or heterocycle (containing 0 - 3 N, O, or S); G = [C(R4)2]n, [C(R4)2]n-NR3, [C(R4)2]nO, [C(R4)2]nS, [CR4:CR4]n; X = [C(R4)2]nCONR3[C(R4)2]n, [C(R4)2]nNR3CO[C(R4)2]n, [C(R4)2]nNR3[C(R4)2]n, [C(R4)2]nO[C(R4)2]n, [C(R4)2]nC(:O)[C(R4)2]n, [C(R4)2]nCO2[C(R4)2]n; Y = alkylene, cycloalkylene, heterodiyl, aryldiyl; T = mono- or binuclear, (un)substituted aromatic carbocycle or heterocycle (containing 0 - 3 N, O, or S); A = (un)branched C1-10-alkyl (optionally containing, O, S or CH:CH in the chain and replacing 1 - 7 H with F); n = 0 - 2; o = 1 - 3], their derivs., solvates, salts and stereoisomers, for the prophylaxis and/or therapy of thromboembolic illnesses. Thus, proline derivative II was prepared from N-Boc-D-proline via amidation with 4-(4-aminophenyl)morpholin-3-one in DMF containing 1-hydroxybenzotriazole hydrate, N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride and N-methylmorpholine, N-deprotection with aqueous HClin dioxane and carbamylation with 4-ClC6H4NCO in CH2Cl2 containing Et3N. The receptor binding activity of II was determined [IC50 = 1.8 x 10-8 M vs. FXa; IC50 = 2.3 x 10-8 M vs. TF/FVIIa].

L44 ANSWER 7 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1075769 HCAPLUS Full-text
DOCUMENT NUMBER: 143:347450
TITLE: Synthesis of prolinyl derivatives for use in the treatment of thromboembolic diseases or tumors
INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleave, Johannes
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

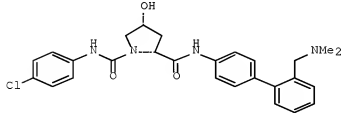
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005092849	A1	20051006	WO 2005-EP2306	20050304
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 102004014945	A1	20051013	DE 2004-102004014945	20040326
AU 2005225489	A1	20051006	AU 2005-225489	20050304
CA 2561057	A1	20051006	CA 2005-2561057	20050304
EP 1735279	A1	20061227	EP 2005-715737	20050304
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, LV				
CN 1938269	A	20070328	CN 2005-80009735	20050304
BR 2005009174	A	20070918	BR 2005-9174	20050304
JP 2007530469	T	20071101	JP 2007-504284	20050304
IN 2006KN02397	A	20070525	IN 2006-KN2397	20060824
MX 2006PA10771	A	20061215	MX 2006-PA10771	20060920
KR 2007010131	A	20070122	KR 2006-719772	20060925
US 20070135507	A1	20070614	US 2006-594024	20060925
PRIORITY APPLN. INFO.:			DE 2004-102004014945A	20040326
			WO 2005-EP2306 W	20050304

OTHER SOURCE(S): MARPAT 143:347450

GI



I



II

AB The invention relates to title compds., e.g. (I), which are inhibitors of coagulation factors Xa and VIIa and can be used for the prophylaxis and/or treatment of thromboembolic diseases and for the treatment of tumors (no data). Thus, (II) was prepared by condensation of (2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxylic acid 1-tert-Bu ester with 4'-amino-N,N-

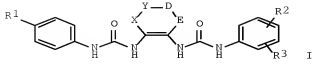
dimethyl-[1,1'-biphenyl]-2-methanamine, followed by condensation with 4-nitrophenyl chloroformate and 4-chloroaniline, to give II (no yield). Sixteen title compds. are claimed, and formulations for administration (e.g., injections, suppositories, etc.) are given.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 8 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:732627 HCAPLUS Full-text
DOCUMENT NUMBER: 143:211919
TITLE: Preparation of heterocyclic urea derivatives as coagulation factor Xa inhibitors.
INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005073201	A1	20050811	WO 2005-EP83	20050107
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 102004004731	A1	20050818	DE 2004-102004004731	20040130
AU 2005209362	A1	20050811	AU 2005-209362	20050107
CA 2554911	A1	20050811	CA 2005-2554911	20050107
EP 1709017	A1	20061011	EP 2005-700739	20050107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
CN 1914184	A	20070214	CN 2005-80003152	20050107
BR 2005007165	A	20070626	BR 2005-7165	20050107
JP 2007519645	T	20070719	JP 2006-549951	20050107
IN 2006KN01699	A	20070511	IN 2006-KN1699	20060620
MX 2006PA08347	A	20060926	MX 2006-PA8347	20060724
US 20070161623	A1	20070712	US 2006-587855	20060728

PRIORITY APPLN. INFO.: DE 2004-102004004731A 20040130
WO 2005-EP83 W 20050107
OTHER SOURCE(S): CASREACT 143:211919; MARPAT 143:211919
GI



I

AB Title compds. [I; XYDE = (substituted) CH:CHCH:CH, N:CHCH:CH, N:CHN:CH, NHCOCH:CH, CH:CHN:CH, etc.; R1 = halo, C.tplbond.CH, C.tplbond.CA, OH, OA; R2 = H, halo, A; R3 = (substituted) 2-oxo-1H-pyridin-1-yl, 2-oxo-1H-pyrazin-1-yl, 2-oxopiperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-iminopiperidin-1-yl, 2-caprolactam-1-yl, etc.; A = (fluoro- and/or chloro-substituted) (cyclo)alkyl], were prepared Thus, 4-(4-amino-2- methylphenyl)morpholin-3-one in CH2Cl2 was treated with 4-nitrophenyl chloroformate and pyridine followed by stirring for 1 h. 1-(2-Amino-4-hydroxyphenyl)-3-(4-chlorophenyl)urethane (preparation given) and ethyldiisopropylamine were added followed by stirring for 20 h to give 18% 1-(4-chlorophenyl)-3-[4-hydroxy-2-[3-[3-methyl-4-(3-oxomorpholin-4-yl)phenyl]ureido]phenyl]urea. The latter showed FXa receptor affinity with IC500 = 12.0 nM.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 9 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:564637 HCAPLUS Full-text

DOCUMENT NUMBER: 143:97636

TITLE: Synthesis of prolinylarylacetamides as coagulation factor Xa inhibitors for use in the prevention or treatment of thromboembolic diseases or tumors

INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes

PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany

SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

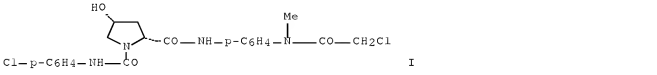
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005058817	A1	20050630	WO 2004-EP13509	20041126
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10358814	A1	20050721	DE 2003-10358814	20031216
AU 2004299197	A1	20050630	AU 2004-299197	20041126
CA 2549589	A1	20050630	CA 2004-2549589	20041126
EP 1697318	A1	20060906	EP 2004-820404	20041126
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
CN 1894210	A	20070110	CN 2004-80037698	20041126
BR 2004017630	A	20070327	BR 2004-17630	20041126
JP 2007513988	T	20070531	JP 2006-544256	20041126
IN 2006KN01579	A	20070504	IN 2006-KN1579	20060608
MX 2006PA06740	A	20060818	MX 2006-PA6740	20060614

US 20070185189	A1	20070809	US 2006-583094		20060615
PRIORITY APPLN. INFO.:			DE 2003-10358814	A	20031216
			WO 2004-EP13509	W	20041126

OTHER SOURCE(S): MARPAT 143:97636
GI



I

AB Title compds., e.g. (I), are claimed as inhibitors of coagulation factor Xa and are claimed for use for the prophylaxis and/or therapy of thromboembolic diseases and in the treatment of tumors, as well as kits containing the compds. of interest. Thus, the title compds. were prepared, e.g., by condensation of (2R,4R)-1-(4-chlorophenylcarbamoyl)-4- hydroxyproline and N-(4-aminophenyl)2-dimethylamino-N-Me acetamide in DMF using N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride as condensing agent. In pharmacol. testing, I had receptor affinity IC50 values of 17.0 nM and 25.0 M using FXa and TF/FVIIa receptors, resp. (no details given). Various formulations for administering the title compds. therapeutically are given.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 10 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2005:540568 HCAPLUS Full-text
DOCUMENT NUMBER:	143:78086
TITLE:	Preparation of urea/carbamate derivatives as inhibitors of coagulation factor Xa for treatment of thromboembolic disorders
INVENTOR(S):	Cezanne, Bertram; Dorsch, Dieter; Mederski, Werner; Tsaklakidis, Christos; Gleitz, Johannes
PATENT ASSIGNEE(S):	Merck Patent G.m.b.H., Germany
SOURCE:	PCT Int. Appl., 80 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	German
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005056528	A1	20050623	WO 2004-EP13202	20041119

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

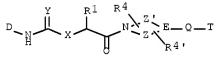
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10358539	A1	20050707	DE 2003-10358539	20031215
AU 2004296956	A1	20050623	AU 2004-296956	20041119
CA 2549548	A1	20050623	CA 2004-2549548	20041119
EP 1694643	A1	20060830	EP 2004-820053	20041119
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, IS				
CN 1890216	A	20070103	CN 2004-80036500	20041119
BR 2004017153	A	20070306	BR 2004-17153	20041119
JP 2007513987	T	20070531	JP 2006-544246	20041119
IN 2006KN01578	A	20070504	IN 2006-KN1578	20060608
MX 2006PA06593	A	20060731	MX 2006-PA6593	20060609
US 20070123509	A1	20070531	US 2006-582850	20060614

PRIORITY APPLN. INFO.: DE 2003-10358539 A 20031215
WO 2004-EP13202 W 20041119

OTHER SOURCE(S): CASREACT 143:78086; MARPAT 143:78086

GI



I

AB Title compds. I [D = halo, alkoxy, etc.; X = amino, O; Y = O, S, amino, etc.; R1 = H, aryl, heteroaryl, etc.; E = CH, N; Z, Z' = acyl, etc.; Q = O, amino, acyl, etc.; R4-4' = A, OH, alkoxy; T = (hetero)cyclyl, etc.] are prepared For instance, (R)-N-(4-chlorophenyl)-N'-[2-[4-(4- fluorophenyl)piperazin-1-yl]-2-oxo-1-phenylethyl]urea (II) is prepared in 3 steps from 1-methyl-4,4'-bipiperidinyl, (R)-N-(tert- butoxycarbonyl)phenylglycine and 4-chlorophenylisocyanate. II has IC50 = 6 x 10-9 M for Factor Xa. I are inhibitors of coagulation factor Xa and can be used for the prophylaxis and/or the treatment of thromboembolic diseases and for treating tumors.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

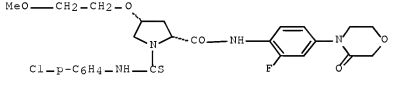
L44 ANSWER 11 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:1125507 HCAPLUS Full-text
DOCUMENT NUMBER: 143:387379
TITLE: Synthesis of thiocarbamoylproline derivatives for use as coagulation factor inhibitors in the prevention or treatment of thromboembolic diseases or tumors
INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes
PATENT ASSIGNEE(S): Merck Patent GmbH, Germany
SOURCE: Ger. Offen., 19 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 102004016605	A1	20051020	DE 2004-102004016605	20040403
WO 2005097783	A1	20051020	WO 2005-EP2745	20050315
WO 2005097783	A8	20070419		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, AP, EA, EP, OA

PRIORITY APPLN. INFO.: DE 2004-102004016605A 20040403
OTHER SOURCE(S): MARPAT 143:387379
GI



I

AB Title compds., e.g. (I), their stereoisomeric forms and physiol. acceptable salts, are claimed for use as inhibitors of coagulation factor Xa or VIIa in the prevention or treatment of thromboembolic illnesses or tumors. Thus, I was prepared by reaction Boc-protected (2R,4R)-4-(2- methoxy)ethoxyproline with 4-(4-amino-3-fluorophenyl)-morpholin-3-one hydrochloride, treating the resulting product with 4N HCl to give the deprotected HCl salt, and condensing this with 4-chlorophenyl- isothiocyanate. In affinity tests with FXa and TF/FVIIa receptors (no details given), I had IC50 of 4.1 and 4.0 x 10-9, resp.

L44 ANSWER 12 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1124627 HCAPLUS Full-text
DOCUMENT NUMBER: 142:74838
TITLE: Preparation of pyrrolidin-1,2-dicarboxylic acids and related compounds as coagulation factor Xa and factor VIIa inhibitors
INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004110433	A1	20041223	WO 2004-EP5717	20040527

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE	10327428	A1	20050105	DE 2003-10327428	20030618
DE	10329457	A1	20050120	DE 2003-10329457	20030701
AU	2004246766	A1	20041223	AU 2004-246766	20040527
CA	2529453	A1	20041223	CA 2004-2529453	20040527
EP	1633346	A1	20060315	EP 2004-735007	20040527
EP	1633346	B1	20060823		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

BR	2004011466	A	20060711	BR 2004-11466	20040527
CN	1809346	A	20060726	CN 2004-80016955	20040527
AT	337000	T	20060915	AT 2004-735007	20040527
JP	2006527708	T	20061207	JP 2006-515798	20040527
ES	2271894	T3	20070416	ES 2004-735007	20040527
IN	2005KN02399	A	20070727	IN 2005-KN2399	20051128
MX	2005PA13536	A	20060309	MX 2005-PA13536	20051213
US	20070093472	A1	20070426	US 2005-561227	20051219

PRIORITY APPLN. INFO.: DE 2003-10327428 A 20030618
DE 2003-10329457 A 20030701
WO 2004-EP5717 W 20040527

OTHER SOURCE(S): MARPAT 142:74838
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R = H, X, A, etc.; R1 = H, =O, halo, etc.; R2 = H, halo, A; R3 = (un)substituted aromatic heterocycle containing 1-4 N, O, S atoms; X = aryl, arylalkyl, het, etc.; A = (un)substituted cycloalkyl] and their pharmaceutically acceptable salts and formulations were prepared For example, condensation of proline II, e.g., prepared from BOC-methoxyproline in 3-steps, and 4-nitrophenylchloroformate and 4-ethynylaniline afforded claimed pyrrolidinyldicarboxylic III in 40% yield. In coagulation factor Xa receptor affinity binding assays, 14-examples of compds. I exhibited IC50 values ranging from 1.1-4.8 nM, i.e., the IC50 value of pyrrolidinyldicarboxylic III was 1.3 nM. Compds. I are claimed to be useful as factor Xa and factor VIIa inhibitors for the treatment of thromboembolic diseases.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

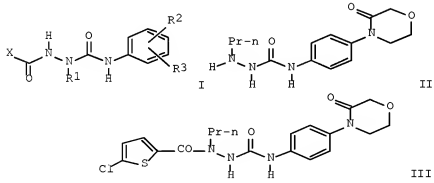
L44 ANSWER 13 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1080898 HCAPLUS Full-text
DOCUMENT NUMBER: 142:56358
TITLE: Preparation of aroylsemicarbazides as factor Xa inhibitors for the treatment of thromboembolic diseases
INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004108718	A1	20041216	WO 2004-EP5088	20040512
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10325962	A1	20041223	DE 2003-10325962	20030607
AU 2004245187	A1	20041216	AU 2004-245187	20040512
CA 2528233	A1	20041216	CA 2004-2528233	20040512
EP 1633745	A1	20060315	EP 2004-732283	20040512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
BR 2004010617	A	20060620	BR 2004-10617	20040512
CN 1802370	A	20060712	CN 2004-80015854	20040512
JP 2006527217	T	20061130	JP 2006-515768	20040512
IN 2005KN02382	A	20061027	IN 2005-KN2382	20051125
MX 2005PA13035	A	20060302	MX 2005-PA13035	20051202
US 20060241111	A1	20061026	US 2006-559385	20060621

PRIORITY APPLN. INFO.: DE 2003-10325962 A 20030607
WO 2004-EP5088 W 20040512

GI



AB Title compds. I [X = Het; Het = bicyclic aromatic heterocycle with 1-3 N, O, or S atoms; R1 = A, S(O)mA, Ph, etc.; R2 = H, halo, A; A = H, (un)substituted cycloalkyl; R3 = 2-oxopiperidin-1-yl, 2-oxopyrrolidin-1- yl, 2-oxo-1H-pyridin-1-yl, etc.] and their pharmaceutically acceptable salts and formulations were prepared For example, coupling of amine II, i.e., prepared from 4-(4-aminophenyl)morpholin-3-one in 4-steps, and 5-chlorothiophen-2-carboxylic acid

afforded aroylsemicarbazide III in 51% yield. In coagulation factor Xa receptor affinity binding assays, 3-examples of compds. I exhibited IC50 values ranging from 87-390 nM, i.e., the IC50 value of aroylsemicarbazide III was 390 nM. Compds. I are claimed to be useful for the treatment of thromboembolic diseases.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

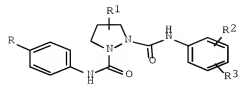
L44 ANSWER 14 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:857592 HCAPLUS Full-text
DOCUMENT NUMBER: 141:332196
TITLE: Preparation of pyrazolidine-1,2-dicarboxamides as Factor Xa inhibitors for the treatment of thrombosis
INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes
PATENT ASSIGNEE(S): Merck Patent GmbH, Germany
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004087696	A1	20041014	WO 2004-EP2407	20040309
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10315377	A1	20041014	DE 2003-10315377	20030403
DE 10329295	A1	20050203	DE 2003-10329295	20030630
DE 10336570	A1	20050224	DE 2003-10336570	20030808
AU 2004226281	A1	20041014	AU 2004-226281	20040309
CA 2520894	A1	20041014	CA 2004-2520894	20040309
EP 1608645	A1	20051228	EP 2004-718641	20040309
EP 1608645	B1	20070502		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
BR 2004008444	A	20060404	BR 2004-8444	20040309
JP 2006522038	T	20060928	JP 2006-504604	20040309
US 20060183742	A1	20060817	US 2005-551559	20051003
IN 2005KN02183	A	20070323	IN 2005-KN2183	20051103

PRIORITY APPLN. INFO.:

DE 2003-10315377	A	20030403
DE 2003-10329295	A	20030630
DE 2003-10336570	A	20030808
WO 2004-EP2407	W	20040309

OTHER SOURCE(S): MARPAT 141:332196
GI



I

AB Title compds. [I; R = H, A, ACO, halo, C.tplbond.CA, C.tplbond.CCOA; R1 = H, O, halo, OH, OA, ACO2, ACONH, ACONA, N3, NH2, NO2, CO2H, CO2A, CONH2, CONHA, allyloxy, propargyloxy, benzyloxy, :NOH, :CF2, etc.; R2 = H, halo, A; R3 = (unsatd.) (substituted) heterocyclyl; A = (fluoro and/or chloro-substituted) (cyclo)alkyl], were prepared Thus, pyrazolidine-1,2- dicarboxylic acid 1-[(4-ethynylphenyl)amide]-2-[[3-chloro-4-(3- oxomorpholin-4-yl)phenyl]amide] [preparation from 4-(4-amino-2- chlorophenyl)morpholin-3-one, tert-Bu pyrazolidine-1-carboxylate, and 4-ethynylaniline given] bound to Factor Xa receptors with IC50 = 75 nM.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 15 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:857591 HCAPLUS Full-text

DOCUMENT NUMBER: 141:314626

TITLE: Method for the production of pyrrolidine-1,2-dicarboxylic acid-1-(phenyl(-amide))-2-(phenyl(-amide)) derivatives and 1-(phenylcarbamoyl)-pyrrolidine-2-carboxylic acid derivatives as intermediate products

INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes

PATENT ASSIGNEE(S): Merck Patent GmbH, Germany

SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 5

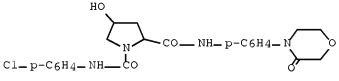
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004087695	A1	20041014	WO 2004-EP2405	20040309
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10315377	A1	20041014	DE 2003-10315377	20030403
DE 10327428	A1	20050105	DE 2003-10327428	20030618
DE 10329295	A1	20050203	DE 2003-10329295	20030630
DE 10329457	A1	20050120	DE 2003-10329457	20030701

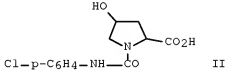
DE 10334174	A1	20050217	DE 2003-10334174		20030726
AU 2004226280	A1	20041014	AU 2004-226280		20040309
CA 2520893	A1	20041014	CA 2004-2520893		20040309
EP 1608646	A1	20051228	EP 2004-718646		20040309
EP 1608646	B1	20070711			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK					
BR 2004008888	A	20060411	BR 2004-8888		20040309
JP 2006522037	T	20060928	JP 2006-504602		20040309
EP 1760081	A1	20070307	EP 2006-22891		20040309
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, LT, LV					
US 20060211692	A1	20060921	US 2005-551670		20050930
IN 2005KN02182	A	20060929	IN 2005-KN2182		20051103
PRIORITY APPLN. INFO.:			DE 2003-10315377	A	20030403
			DE 2003-10327428	A	20030618
			DE 2003-10329295	A	20030630
			DE 2003-10329457	A	20030701
			DE 2003-10334174	A	20030726
			EP 2004-718646	A3	20040309
			WO 2004-EP2405	W	20040309

OTHER SOURCE(S): CASREACT 141:314626; MARPAT 141:314626

GI



I



II

AB The invention relates to a method for the production of title compds., e.g. (I), and intermediate products, e.g. (II) for the production of I. Thus, cis-hydroxy-D-proline was reacted with 4-chlorophenylisocyante in NaHCO3 at 80° for 5 h. to give after workup 81.8% (R,R)-II. II was then reacted with 4-(3-oxo-4-morpholinyl)aniline in THF with 2-ethoxy-1(2H)-quinolinecarboxylic acid Et ester (EEDQ) as coupling agent at room temperature for 20 h to give, after workup, 69% (R,R)-I.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 16 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:857551 HCAPLUS Full-text

DOCUMENT NUMBER: 141:350179

TITLE: Preparation of azolidinedicarboxamides and related compounds as Factor Xa and Factor VIIa inhibitors

INVENTOR(S): Tsaklakidis, Christos; Dorsch, Dieter; Mederski, Werner; Cezanne,

Bertram; Gleitz, Johannes

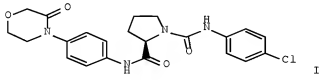
PATENT ASSIGNEE(S): Merck Patent GmbH, Germany
SOURCE: PCT Int. Appl., 162 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004087646	A2	20041014	WO 2004-EP2350	20040308
WO 2004087646	A3	20050106		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10315377	A1	20041014	DE 2003-10315377	20030403
DE 10329295	A1	20050203	DE 2003-10329295	20030630
AU 2004226278	A1	20041014	AU 2004-226278	20040308
CA 2521069	A1	20041014	CA 2004-2521069	20040308
BR 2004008420	A	20060321	BR 2004-8420	20040308
JP 2006522033	T	20060928	JP 2006-504581	20040308
EP 1720844	A2	20061115	EP 2004-718299	20040308
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, LT, LV				
IN 2005KN01684	A	20070727	IN 2005-KN1684	20050823
US 20060183739	A1	20060817	US 2005-551557	20051003

PRIORITY APPLN. INFO.:

DE 2003-10315377	A	20030403
DE 2003-10329295	A	20030630
US 2003-483897P	P	20030702
WO 2004-EP2350	W	20040308

OTHER SOURCE(S): MARPAT 141:350179
GI



I

AB R1R2(TYX)EWCOGD [R1, R2 = H, O, halo, A, ethynyl, OR3, N(R3)2, NO2, cyano, N3, CO2R3, CON(R3)2, etc.; R3 = H, A, HC.tplbond.CCH2, MeC.tplbond.CCH2, CH2CH(OH)CH2OH, etc.; R4 = H, A; W = N, C, CR3; E = atoms to form a 3-7 membered (heterocyclic) ring optionally containing a double bond; D = mono- or dinuclear (substituted) (hetero)aryl; G = [C(R4)2]n, [C(R4)2]nNR3, [C(R4)2]nO, [C(R4)2]nS, etc.; n = 0-2; X = [C(R4)2]nCO[C(R4)2]n, [C(R4)2]n,NR3[C(R4)2]n,

[C(R4)2]nNR3CO[C(R4)2]n, etc.; Y = alkylene, cycloalkylene, heterocyclylene, arenediyl; T = substituted mono- or dinuclear carbocyclyl, heterocyclyl; A = (fluoro-substituted) alkyl optionally interrupted by O, S, CH:CH], were prepared Thus, title compound (I) [preparation from 4-(4-aminophenyl)morpholin-3-one, Boc-D-proline, and 4-chlorophenyl isocyanate given] bound to Factor Xa receptors with IC50 = 1.8 + 10-8 M.

L44 ANSWER 17 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:20490 HCAPLUS Full-text

DOCUMENT NUMBER: 140:77148

TITLE: Preparation of N-[4-(thiooxoheterocyclyl)phenyl]-2-phenyl-2H-pyrazole-3-carboxamides and corresponding imino-heterocyclyl derivatives as inhibitors of the coagulation factors Xa and/or VIIa for treating thrombosis

INVENTOR(S): Cezanne, Bertram; Dorsch, Dieter; Mederski, Werner; Tsaklakidis, Christos; Gleitz, Johannes; Barnes, Christopher

PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany

SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004002477	A1	20040108	WO 2003-EP5898	20030605
WO 2004002477	A8	20040415		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10229070	A1	20040115	DE 2002-10229070	20020628
CA 2491271	A1	20040108	CA 2003-2491271	20030605
AU 2003238475	A1	20040119	AU 2003-238475	20030605
EP 1517685	A1	20050330	EP 2003-732540	20030605
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005535630	T	20051124	JP 2004-516575	20030605
EP 1679073	A1	20060712	EP 2006-157	20030605
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, SK				
US 20050203127	A1	20050915	US 2004-519356	20041228

PRIORITY APPLN. INFO.: DE 2002-10229070 A 20020628
EP 2003-732540 A3 20030605
WO 2003-EP5898 W 20030605

OTHER SOURCE(S): MARPAT 140:77148

GI

AB Title compds. [I; D = (N-, O-, S-interrupted) (substituted) C3-4 alkylene; M = Ph, aromatic heterocyclyl; R1, R2 = H, halo, (branched) (interrupted) (substituted) alkyl, NO2, cyano, OR3, N(R3)2, CO2R3, CON(R3)2, C(:S)N(R3)2, etc.; R3 = H, (branched) (interrupted) (substituted) alkyl, etc.; W = (substituted) (bi)cyclic aromatic (hetero)cyclyl; X = CONR3, CONR3C(R4)2, C(R4)2NR3, etc.; R4 = H, (branched) (interrupted) (substituted) alkyl; Y = alkylene, cycloalkylene, heterodiyl, aryldiyl; T = (substituted) (bi)cyclic aromatic heterocyclyl], were prepared Thus, 333 mg (3-[5-(4-[2-iminopyrrolidin-1-yl]phenylcarbamoyl)-3-trifluoromethylpyrazol- 1-yl]benzyl)carbamic acid tert-Bu ester (preparation given) in EtOH was treated with HCl in ether to give 289 mg N-[4-(2-iminopyrrolidin-1-yl)phenyl]-1-(3-aminomethylphenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide. The latter gave affinity to the receptor Xa with IC50 = 9,6·10-9 M and to the receptor VIIa with IC50 = 2,3·10-8 M.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 18 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:841766 HCAPLUS Full-text

DOCUMENT NUMBER: 141:332202

TITLE: Preparation of azolidinecarboxamides as antithrombotics and anticancer drugs.

INVENTOR(S): Tsaklakidis, Christos; Dorsch, Dieter; Mederski, Werner; Cezanne, Bertram; Gleitz, Johannes

PATENT ASSIGNEE(S): Merck Patent GmbH, Germany

SOURCE: Ger. Offen., 47 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 5

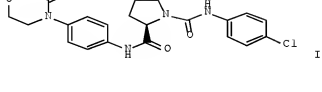
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10315377	A1	20041014	DE 2003-10315377	20030403
AU 2004226278	A1	20041014	AU 2004-226278	20040308
CA 2521069	A1	20041014	CA 2004-2521069	20040308
WO 2004087646	A2	20041014	WO 2004-EP2350	20040308
WO 2004087646	A3	20050106		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
BR 2004008420	A	20060321	BR 2004-8420	20040308

CN 1771237	A	20060510	CN 2004-80009354		20040308
JP 2006522033	T	20060928	JP 2006-504581		20040308
EP 1720844	A2	20061115	EP 2004-718299		20040308
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, LT, LV					
AU 2004226280	A1	20041014	AU 2004-226280		20040309
AU 2004226281	A1	20041014	AU 2004-226281		20040309
CA 2520893	A1	20041014	CA 2004-2520893		20040309
CA 2520894	A1	20041014	CA 2004-2520894		20040309
WO 2004087695	A1	20041014	WO 2004-EP2405		20040309
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
WO 2004087696	A1	20041014	WO 2004-EP2407		20040309
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
EP 1608645	A1	20051228	EP 2004-718641		20040309
EP 1608645	B1	20070502			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK					
EP 1608646	A1	20051228	EP 2004-718646		20040309
EP 1608646	B1	20070711			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK					
BR 2004008444	A	20060404	BR 2004-8444		20040309
BR 2004008888	A	20060411	BR 2004-8888		20040309
CN 1771248	A	20060510	CN 2004-80009374		20040309
CN 1771249	A	20060510	CN 2004-80009463		20040309
JP 2006522037	T	20060928	JP 2006-504602		20040309
JP 2006522038	T	20060928	JP 2006-504604		20040309
AT 361296	T	20070515	AT 2004-718641		20040309
AT 366732	T	20070815	AT 2004-718646		20040309
ES 2285444	T3	20071116	ES 2004-718641		20040309
ES 2287708	T3	20071216	ES 2004-718646		20040309
IN 2005KN01684	A	20070727	IN 2005-KN1684		20050823
US 20060211692	A1	20060921	US 2005-551670		20050930
US 20060183739	A1	20060817	US 2005-551557		20051003
US 20060183742	A1	20060817	US 2005-551559		20051003
IN 2005KN02182	A	20060929	IN 2005-KN2182		20051103
IN 2005KN02183	A	20070323	IN 2005-KN2183		20051103
PRIORITY APPLN. INFO.:			DE 2003-10315377	A	20030403
			DE 2003-10327428	A	20030618
			DE 2003-10329295	A	20030630

	DE 2003-10329457	A	20030701
	US 2003-483897P	P	20030702
	DE 2003-10334174	A	20030726
	DE 2003-10336570	A	20030808
	WO 2004-EP2350	W	20040308
	WO 2004-EP2405	W	20040309
	WO 2004-EP2407	W	20040309

OTHER SOURCE(S): MARPAT 141:332202
GI



I

AB R1R2(TYX)EWCOGD [R1, R2 = H, O, halo, A, ethynyl, OR3, NO2, cyano, N3, CO2R3, CON(R3)2, NR3COA, NR3SO2A, etc.; R1R2 = toms to form a bicyclic or spirocyclic (heterocyclic) ring; R3 = H, A, etc.; R4 = H, A; W = N, CR3, C; E = atoms to form a 3-7 membered (double bond containing) (heterocyclic) ring with W; G = [C(R4)2]n, [C(R4)2]nNR3, [C(R4)2]nO, [C(R4)2]nS; X = [C(R4)2]nCONR3[C(R4)2]n, [C(R4)2]nON[C(R4)2]n, etc.; Y = alkylene, cycloalkylene, (substituted) heterocyclylene, arylene; T = mono- or bicyclic substituted (unsatd.) (hetero)cyclyl; A = (fluoro-substituted) alkylene optionally interrupted by O, S, CH:CH; n = 0-2], were prepared Thus, title compound (I) (prepared from 4-(4-aminophenyl)morpholin-3-one, Boc-D-proline, and 4-chlorophenyl isocyanate), bound to Factor Xa receptors with IC50 = 1.8 + 10-8 M.

L44 ANSWER 19 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:738402 HCAPLUS Full-text
DOCUMENT NUMBER: 141:243828
TITLE: Synthesis of amino acid ethylene derivatives for use as coagulation factor Xa inhibitors for treatment of disease
INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Dorsch, Dieter; Cezanne, Bertram; Gleitz, Johannes; Van Amsterdam, Christoph
PATENT ASSIGNEE(S): Merck Patent GmbH, Germany
SOURCE: Ger. Offen., 19 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10308907	A1	20040909	DE 2003-10308907	20030228
AU 2004215708	A1	20040910	AU 2004-215708	20040130
CA 2517391	A1	20040910	CA 2004-2517391	20040130
WO 2004076429	A1	20040910	WO 2004-EP817	20040130

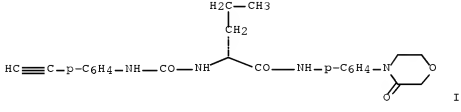
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,

LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1597244	A1	20051123	EP 2004-706669		20040130
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2004007865	A	20060301	BR 2004-7865		20040130
CN 1753882	A	20060329	CN 2004-80005443		20040130
JP 2006519188	T	20060824	JP 2006-501655		20040130
MX 2005PA09002	A	20051018	MX 2005-PA9002		20050824
US 20060084648	A1	20060420	US 2005-547130		20050826
PRIORITY APPLN. INFO.:			DE 2003-10308907	A	20030228
			WO 2004-EP817	W	20040130

OTHER SOURCE(S): MARPAT 141:243828

GI



I

AB Title compds., e.g., (I), were prepared and tested for use as inhibitors of coagulation factors Xa and VIIa, for treatment of thromboembolic illnesses or tumors. Thus, Fmoc-D-Nva-OH (Nva = norvaline) was reacted with 4-(3-oxo-4-morpholinyl)aniline, the intermediate Fmoc-deprotected, and the product coupled with 4-ethynylaniline to give I. I had IC50 affinities for factor Xa or VIIa receptors, resp., of 2.5 x 10-8 M and 8.8 x 10-8 M (no exptl. details given).

L44 ANSWER 20 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

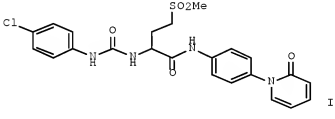
ACCESSION NUMBER:	2004:605492 HCAPLUS Full-text
DOCUMENT NUMBER:	141:157122
TITLE:	Preparation of ureidoazinylalkanamides as inhibitors of blood coagulation Factor VIIa and Xa.
INVENTOR(S):	Dorsch, Dieter; Cezanne, Bertram; Mederski, Werner; Tsaklakidis, Christos; Gleitz, Johannes; Van Amsterdam, Christoph
PATENT ASSIGNEE(S):	Merck Patent GmbH, Germany
SOURCE:	Ger. Offen., 25 pp. CODEN: GWXXBX
DOCUMENT TYPE:	Patent
LANGUAGE:	German
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10302500	A1	20040729	DE 2003-10302500	20030123

AU 2004205354	A1	20040805	AU 2004-205354		20040108
CA 2514100	A1	20040805	CA 2004-2514100		20040108
WO 2004065369	A1	20040805	WO 2004-EP61		20040108
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ					
EP 1585730	A1	20051019	EP 2004-700684		20040108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2004006844	A	20051213	BR 2004-6844		20040108
CN 1741996	A	20060301	CN 2004-80002520		20040108
JP 2006516566	T	20060706	JP 2006-500530		20040108
MX 2005PA07715	A	20050930	MX 2005-PA7715		20050720
US 20060074072	A1	20060406	US 2005-543109		20050722
ZA 2005006730	A	20060531	ZA 2005-6730		20050822
PRIORITY APPLN. INFO.:			DE 2003-10302500	A	20030123
			WO 2004-EP61	A	20040108

OTHER SOURCE(S): MARPAT 141:157122

GI



I

AB DNHCOXCHR1CONHWYT [D = (substituted) Ph, pyridyl; R1 = (substituted) A; W = [C(R3)2]n; X = NR3, O; Y = alkylene, heterocyclylene, arylene; R2 = H, A, [C(R3)2]nAr, etc.; Ar = (substituted) Ph; R3 = H, A; T = N(R2)2, (substituted) saturated, unsatd., or aromatic carbocyclyl, heterocyclyl; A = (O-, S, or CH:CH-interrupted) (fluorinated) alkyl; n = 0-2], were prepared Thus, 2-amino-4-methylsulfonylbutyric acid in H2O at 80° was treated with 4-chlorophenyl isocyanate followed by stirring for 1 h to give 2-[3-(4-chlorophenyl)ureido]-4-methanesulfonylbutyric acid. This was stirred with 1-(4-aminophenyl)-1H-pyridin-2-one and TBTU in DMF for 24 h to give title compound (I). I bound to Factor Xa receptors with IC50 = 2.8 + 10-8 M.

L44 ANSWER 21 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

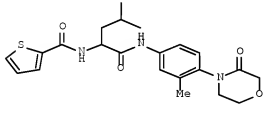
ACCESSION NUMBER:	2004:450507 HCAPLUS Full-text
DOCUMENT NUMBER:	141:7126
TITLE:	Preparation of heterocyclylamides as inhibitors of Factor VIIA and Xa.
INVENTOR(S):	Dorsch, Dieter; Cezanne, Bertram; Mederski, Werner; Tsaklakidis, Christos; Wurziger, Hanns; Gleitz, Johannes; van Amsterdam, Christoph
PATENT ASSIGNEE(S):	Merck Patent GmbH, Germany
SOURCE:	Ger. Offen., 26 pp. CODEN: GWXXBX
DOCUMENT TYPE:	Patent
LANGUAGE:	German

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10254336	A1	20040603	DE 2002-10254336	20021121
CA 2506716	A1	20040603	CA 2003-2506716	20031030
WO 2004046138	A1	20040603	WO 2003-EP12080	20031030
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003286145	A1	20040615	AU 2003-286145	20031030
EP 1562939	A1	20050817	EP 2003-776875	20031030
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006512321	T	20060413	JP 2004-552505	20031030
US 20060052376	A1	20060309	US 2005-535246	20050518

PRIORITY APPLN. INFO.: DE 2002-10254336 A 20021121
WO 2003-EP12080 W 20031030

OTHER SOURCE(S): MARPAT 141:7126
GI



I

AB DXNH[C(R1)2]mCONHWYT [D = (substituted) aryl, heteroaryl; X = CO, C(R3)2; W = [C(R3)2]n; R1 = H, (substituted) A; R3 = H, A; A = (fluoro-substituted) alkyl optionally interrupted by O, S, CH:CH; T = mono- or bicyclic (substituted) (unsatd.) (aromatic) carbocyclyl, heterocyclyl; Y = alkylene, cycloalkylene, (hetero)arylene; m = 1, 2; n = 0-2], were prepared for treatment of thrombosis, arteriosclerosis, inflammation, etc. (no data). Thus, (R)-2-[(5-chlorothiophene-2- carbonyl)amino]-4-methylpentanoic acid (preparation given), 4-(4-amino-2-methylphenyl)morpholin-3-one, and TBTU were stirred 18 h in DMF to give title compound (I).

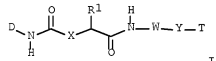
L44 ANSWER 22 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:328850 HCAPLUS Full-text
DOCUMENT NUMBER: 140:357340
TITLE: Preparation of N-(5-chloro-2-thienyl)ureas and related compounds as coagulation factor Xa inhibitors for the treatment of thromboembolic illnesses
INVENTOR(S): Dorsch, Dieter; Czezanne, Bertram;

Mederski, Werner; Tsaklakidis, Christos; Gleitz, Johannes; Barnes, Christopher

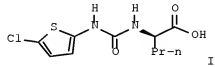
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 28 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10247226	A1	20040422	DE 2002-10247226	20021010
CA 2501706	A1	20040429	CA 2003-2501706	20030918
WO 2004035039	A1	20040429	WO 2003-EP10400	20030918
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003270223	A1	20040504	AU 2003-270223	20030918
EP 1549304	A1	20050706	EP 2003-750577	20030918
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006510604	T	20060330	JP 2004-544033	20030918
US 20060135515	A1	20060622	US 2005-530876	20050411
PRIORITY APPLN. INFO.:			DE 2002-10247226 A	20021010
			WO 2003-EP10400 W	20030918

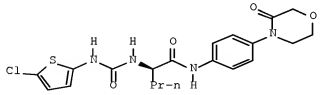
OTHER SOURCE(S): MARPAT 140:357340
GI



I



II



III

AB Title compds. I [D = halo, A, OR2, etc.; X = NR3, O; R1 = H, Ar, cycloalkyl, etc.; R2 = H, A, [C(R3)]n-Ar, etc.; R3 = H, A; W = [C(R3)]n; Y = alkylene, cycloalkylene, Het-diyl (sic), etc.; T = aromatic, heterocyclic; A = OR2, NO2, CN, etc.; n = 0-2] and their pharmaceutically acceptable salts and formulations were prepared For example, coupling of acid II, e.g., prepared from 2-chloro-5-isocyanatothiophene and D-norvaline, and 4-(4-

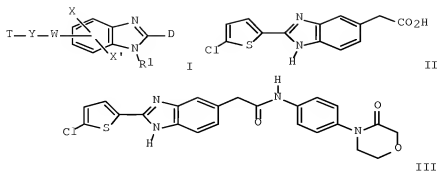
aminophenyl)morpholin-3-one afforded benzimidazole III. In coagulation factor Xa inhibition assays, 2-examples of compds. I exhibited IC50 values ranging from 6.6-19 x 10-8 M, e.g., the IC50 value of benzimidazole III was 1.9 x 10-7 M. Compds. I are claimed useful for the treatment of thromboembolic illnesses and tumors.

L44 ANSWER 23 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:177880 HCAPLUS Full-text
DOCUMENT NUMBER: 140:235708
TITLE: Preparation of benzimidazoles as coagulation factor Xa inhibitors for the treatment of thromboembolic illnesses
INVENTOR(S): Dorsch, Dieter; Cezanne, Bertram; Nederski, Werner; Tsaklakidis, Christos; Glaitz, Johannes; Barnes, Christopher
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 34 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10238002	A1	20040304	DE 2002-10238002	20020820
CA 2496139	A1	20040304	CA 2003-2496139	20030704
WO 2004017963	A1	20040304	WO 2003-EP7180	20030704
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003250890	A1	20040311	AU 2003-250890	20030704
BR 2003013634	A	20050621	BR 2003-13634	20030704
EP 1558247	A1	20050803	EP 2003-792176	20030704
EP 1558247	B1	20080220		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1674893	A	20050928	CN 2003-819835	20030704
JP 2006500369	T	20060105	JP 2004-529997	20030704
AT 386518	T	20080315	AT 2003-792176	20030704
US 20050272740	A1	20051208	US 2005-525001	20050217

PRIORITY APPLN. INFO.: DE 2002-10238002 A 20020820
WO 2003-EP7180 W 20030704

OTHER SOURCE(S): MARPAT 140:235708
GI



I II III

AB Title compds. I [D = halo, A, OR2, etc.; X, X' = N, halo, A, etc.; R1 = H, A; R2 = H, A, [C(R1)]n-Ar', etc.; Y = alkylene, cycloalkylene, Het-diyl (sic), etc.; T = aromatic, heterocyclic; W = [C(R2)2]nCONR2[C(R2)2]n, [C(R2)2]nNR2CO[C(R2)2]n, [C(R2)2]nO[C(R2)2]n, etc.; A = (un)substituted alkyl with provisos; Ar' = (un)substituted Ph e.g., halo, A, OR1, etc.; n = 0-2] and their pharmaceutically acceptable salts and formulations were prepared For example, coupling of acid II, e.g., prepared from 2-chlorothiophen-5-aldehyde in 2-steps, and 4-(4-aminophenyl)morpholin-3- one afforded benzimidazole III. In coagulation factor Xa inhibition assays, 3-examples of compds. I exhibited IC50 values ranging from 1.2-2.3 x 10-7 M, e.g., the IC50 value of benzimidazole III was 2.3 x 10-7 M. Compds. I are claimed useful for the treatment of thromboembolic illnesses and tumors.

L44 ANSWER 24 OF 38 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004530089 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15501047
TITLE: Chlorothiophenecarboxamides as P1 surrogates of inhibitors of blood coagulation factor Xa.
AUTHOR: Mederski Werner W K R; Cezanne Bertram; van Amsterdam Christoph; Buhring Karl-Ulrich; Dorsch Dieter; Gleitz Johannes; Marz Joachim; Tsaklakidis Christos
CORPORATE SOURCE: Merck KGaA, Preclinical Pharmaceutical Research, 64271 Darmstadt, Germany.. mederski@merck.de
SOURCE: Bioorganic & medicinal chemistry letters, (2004 Dec 6) Vol. 14, No. 23, pp. 5817-22.
Journal code: 9107377. ISSN: 0960-894X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200503
ENTRY DATE: Entered STN: 26 Oct 2004
Last Updated on STN: 23 Mar 2005
Entered Medline: 22 Mar 2005

AB Neutral chlorothiophenecarboxamides bearing an amino acid and a substituted aniline were synthesized and investigated for their factor Xa inhibitory activity in vitro. From selected 2-methylphenyl morpholinones the solution properties were determined. The most soluble and active compounds were then investigated in different animal species to compare the pharmacokinetic parameters. This led to a potent, water soluble and orally bioavailable candidate for further development: EMD 495235.

L44 ANSWER 25 OF 38 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004302259 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 15203158
TITLE: Halothiophene benzimidazoles as P1 surrogates of inhibitors of blood coagulation factor Xa.
AUTHOR: Mederski Werner W K R; Dorsch Dieter; Anzali Soheila; Gleitz Johannes; Cezanne Bertram; Tsaklakidis Christos
CORPORATE SOURCE: Merck KGaA, Preclinical Pharmaceutical Research, 64271 Darmstadt, Germany.. mederski@merck.de
SOURCE: Bioorganic & medicinal chemistry letters, (2004 Jul 16) Vol. 14, No. 14, pp. 3763-9.
Journal code: 9107377. ISSN: 0960-894X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 24 Jun 2004
Last Updated on STN: 8 Feb 2005
Entered Medline: 7 Feb 2005

AB Neutral weak halothiophene benzimidazole inhibitors of the serine protease factor Xa were identified via screening of a compound library. The X-ray crystal structure of representative 3a bound to human fXa confirmed the S1 binding mode. Starting from 3a a series of halothiophene benzimidazoles was synthesized and investigated for their factor Xa inhibitory activity. This led to potent and selective achiral inhibitors against fXa such as compounds 9k and 9w.

L44 ANSWER 26 OF 38 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:473432 BIOSIS Full-text
DOCUMENT NUMBER: PREV200510263251
TITLE: Novel solubilizing S4-residues for factor XA inhibitors: Synthesis and structure-activity relationships of 1-aryl-2-imino-pyrrrolidine and -piperidine derivatives.
AUTHOR(S): Cezanne, Bertram [Reprint Author]; Dorsch, Dieter; Mederski, Werner W. K. R.; Tsaklakidis, Christos; Gleitz, Johannes; Anzali, Soheila
CORPORATE SOURCE: Merck KGaA, Preclin Res and Dev, D-64271 Darmstadt, Germany bertram.cezanne@merck.de; dieter.dorsch@merck.de
SOURCE: Abstracts of Papers American Chemical Society, (AUG 22 2004) Vol. 228, No. Part 1, pp. U953.
Meeting Info.: Meeting of the Division of Chemical Toxicology of the American-Chemical-Society held at the 228th National Meeting of the American-Chemical-Society. Philadelphia, PA, USA. August 22 -26, 2004. Amer Chem Soc, Div Chem Toxicol.
CODEN: ACSRAL. ISSN: 0065-7727.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Nov 2005
Last Updated on STN: 16 Nov 2005

L44 ANSWER 27 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:658117 HCAPLUS Full-text

10551670

TITLE: Novel solubilizing S4-residues for factor Xa inhibitors: Synthesis and structure-activity relationships of 1-aryl-2-imino-pyrrolidine and -piperidine derivatives

AUTHOR(S): Cezanne, Bertram; Dorsch, Dieter; Mederski, Werner W. K. R.; Tsaklakidis, Christos; Gleitz, Johannes; Anzali, Soheila

CORPORATE SOURCE: Preclinical Research & Development, Merck KGaA, Darmstadt, 64271, Germany

SOURCE: Abstracts of Papers, 228th ACS National Meeting, Philadelphia, PA, United States, August 22-26, 2004 (2004), MEDI-253. American Chemical Society: Washington, D. C.
CODEN: 69FTZ8

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB Factor Xa is a serine proteinase, which cleaves prothrombin to thrombin, leading to clot formation. It is widely recognized as a very attractive target for the development of new antithrombotic agents. Factor Xa possesses two distinct binding pockets, P1, which has been found to bind hydrophobic chlorophenyl residues well, and P4, which has a more extended shape and binds two-ring S4-residues like biphenyl or heterocyclyl-Ph. In our search for potent and soluble factor Xa inhibitors, we found that compds. with S4-residues bearing a basic cyclic amidine moiety such as 1-aryl-2-imino-pyrrolidine or -piperidine showed both high potency and good aqueous solubility The binding mode of these compds. was studied by X-ray structure anal. of a complex of compound 1 with factor Xa. We will report on the syntheses and biol. properties (in vitro and in vivo) of several factor Xa inhibitors with S4-residues having a cyclic amidine moiety.

L44 ANSWER 28 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:892749 HCAPLUS Full-text

DOCUMENT NUMBER: 139:381378

TITLE: Preparation of carboxylic acid amides as inhibitors of blood-coagulation factor Xa and VIIa

INVENTOR(S): Dorsch, Dieter; Mederski, Werner; Gleitz, Johannes; Cezanne, Bertram; Tsaklakidis, Christos; Barnes, Christopher

PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany

SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093235	A1	20031113	WO 2003-EP3331	20030331

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,

BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10218974	A1	20031127	DE 2002-10218974 20020427
DE 10236868	A1	20040226	DE 2002-10236868 20020812
CA 2483228	A1	20031113	CA 2003-2483228 20030331
AU 2003226755	A1	20031117	AU 2003-226755 20030331
EP 1499591	A1	20050126	EP 2003-747402 20030331

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

JP 2005531547	T	20051020	JP 2004-501374 20030331
US 20050171154	A1	20050804	US 2004-512478 20041026
US 7183277	B2	20070227	

PRIORITY APPLN. INFO.: DE 2002-10218974 A 20020427
DE 2002-10236868 A 20020812
WO 2003-EP3331 W 20030331

OTHER SOURCE(S): MARPAT 139:381378

AB Carboxylic acid amides DNHC(O)CHR1C(O)NHWYT [D = (substituted) Ph, pyridyl, thienyl; X = NR3, O; R1 = H, Ar, Het, cycloalkyl, (substituted) A; W = [C(R3)2]n; Y = alkylene, cycloalkylene, Het-diyl, Ar-diyl; T = (bicyclic) (substituted) heterocyclyl; R3 = H, A; A = (branched) (interrupted) (fluorinated) C1-10 alkyl; Ar = (substituted) Ph, naphthyl, biphenyl; Het = (bicyclic) (substituted) heterocyclyl; n = 0-2], were prepared for treating thrombosis and tumors. Thus, (R)-2-[N-(4- chlorophenyl)-carbamoyloxy]-N-[4-(2-iminopiperidin-1-yl)phenyl]-2- phenylacetamide (preparation given) in HCl was lyophilized to give (R)-2-[N-(4-chlorophenyl)-carbamoyloxy]-N-[4-(2-iminopiperidin-1- yl)phenyl]-2-phenylacetamide hydrochloride. The latter showed affinity to the receptor Xa with IC50 = 5.8·10-8 M and to the receptor VIIa with IC50 = 9.9·10-8 M.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 29 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:818282 HCAPLUS Full-text
DOCUMENT NUMBER: 139:323430
TITLE: Preparation of 2-iminopyrrolidines and related compounds as blood-coagulation factor Xa and VIIa inhibitors for the treatment of tumors and thromboembolic diseases
INVENTOR(S): Cezanne, Bertram; Dorsch, Dieter; Mederski, Werner; Tsaklakidis, Christos; Barnes, Christopher; Gleitz, Johannes
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003084533	A1	20031016	WO 2003-EP2349	20030307

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,

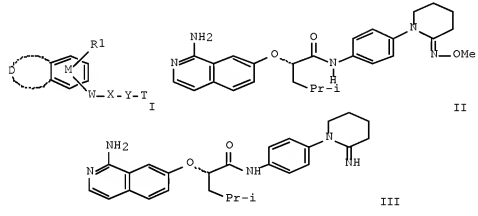
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10214832	A1	20031016	DE 2002-10214832	20020404
CA 2481026	A1	20031016	CA 2003-2481026	20030307
AU 2003214102	A1	20031020	AU 2003-214102	20030307
EP 1490056	A1	20041229	EP 2003-709758	20030307
EP 1490056	B1	20060830		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005528377	T	20050922	JP 2003-581773	20030307
AT 337779	T	20060915	AT 2003-709758	20030307
ES 2271539	T3	20070416	ES 2003-709758	20030307
US 20050176760	A1	20050811	US 2004-510046	20041001

PRIORITY APPLN. INFO.: DE 2002-10214832 A 20020404
WO 2003-EP2349 W 20030307

OTHER SOURCE(S): MARPAT 139:323430

GI



AB Title compds. I [D = (un)saturated 3-4 membered alkylene (sic) with provisos; M = Ph, aromatic heterocycle containing 1-2 N, O, or S atoms; R1 = H, halo, A, etc.; A = (un)substituted alkyl; W = C(R2)2, [(CR2)2]2, OC(R2)2, etc.; R2 = H, A, [C(R3)2]n-Ar, etc.; R3 = H, A; Ar = (un)substituted aryl, e.g., halo, A, OR3, etc.; X = CONR2, CONR2C(R3)2, C(R3)2NR3, etc.; Y = alkylene, cycloalkylene, Het-diyl (sic), etc.; T = (un)substituted aromatic, heteroarom.; n = 0-2] and their pharmaceutically acceptable salts and formulations were prepared For example, Raney-Ni mediated reduction of hydroxyoxime II, e.g., prepared from 7-isoquinolinol in 4-steps, afforded the diacetate salt of 2-iminopiperidine III. In coagulation factor Xa receptor affinity assays, 5-examples of compds. I exhibited IC50 values ranging from 2.7-0.058 μM, e.g., the IC50 value of 2-iminopiperidine III diacetate was 2.7 μM. Compds. I are claimed useful as antithrombotic and antitumor agents.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 30 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:719442 HCAPLUS Full-text
DOCUMENT NUMBER: 139:245786
TITLE: Preparation of semicarbazides as coagulation factor Xa inhibitors for the treatment of thromboembolic diseases

10551670

INVENTOR(S): Mederski, Werner; Ceranna, Bertram ; Tsaklakidis, Christos; Dorsch, Dieter; Barnes, Christopher; Gleitz, Johannes

PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany

SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003074479	A1	20030912	WO 2003-EP1177	20030206
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2478528	A1	20030912	CA 2003-2478528	20030206
AU 2003206852	A1	20030916	AU 2003-206852	20030206
EP 1480948	A1	20041201	EP 2003-704559	20030206
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003008136	A	20050104	BR 2003-8136	20030206
JP 2005519114	T	20050630	JP 2003-572950	20030206
CN 1639115	A	20050713	CN 2003-805144	20030206
MX 2004PA08479	A	20041206	MX 2004-PA8479	20040901
US 20050119316	A1	20050602	US 2004-506801	20040907
ZA 2004007903	A	20050704	ZA 2004-7903	20040930

PRIORITY APPLN. INFO.: DE 2002-10209211 A 20020304
WO 2003-EP1177 W 20030206

OTHER SOURCE(S): MARPAT 139:245786

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R = C(=NH)NH2, OH, OCOOA, etc.; R1 = (un)substituted alkyl; R2 = S(O)pA, S(O)pNHA, CF3, etc.; R3 = H, halo; A = H, ; p = 0-2] and their pharmaceutically acceptable salts and formulations were prepared For example, Michael addition of phenylmagnesium bromide to ketone II, e.g., prepared from 3-fluoro-2'-(methylsulfonyl)-[1,1'-biphenyl]-4-amine in 2-steps, followed by hydroxylamine mediated hydrolysis, afforded claimed N-hydroxycarboximidamide III. In coagulation factor Xa affinity receptor (sic) assays, 3-examples of compds. I exhibited IC50 values ranging from 0.028-3.8 μM, e.g., the IC50 value of N-hydroxycarboximidamide III was 3.8 μM. Compds. I are claimed useful as antimigraine, antithrombotic, antiarteriosclerotic, etc. agents.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

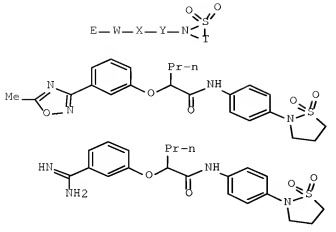
L44 ANSWER 31 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:376636 HCAPLUS Full-text
DOCUMENT NUMBER: 138:385436
TITLE: Preparation of 4-(1,1-dioxido-2-isothiazolidinyl)benzenamines as inhibitors of blood-coagulation factor Xa for the treatment of thromboembolic diseases
INVENTOR(S): Dorsch, Dieter; Cezanne, Bertram; Tsaklakidis, Christos; Mederski, Werner; Gleitz, Johannes; Barnes, Christopher
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003039543	A1	20030515	WO 2002-EP11349	20021010
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10155075	A1	20030522	DE 2001-10155075	20011109
CA 2465713	A1	20030515	CA 2002-2465713	20021010
AU 2002363366	A1	20030519	AU 2002-363366	20021010
AU 2002363366	B2	20071122		
EP 1441726	A1	20040804	EP 2002-802623	20021010
EP 1441726	B1	20061220		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002013680	A	20041026	BR 2002-13680	20021010
HU 2004001983	A2	20050128	HU 2004-1983	20021010
CN 1582148	A	20050216	CN 2002-821919	20021010
JP 2005522412	T	20050728	JP 2003-541834	20021010
AT 348611	T	20070115	AT 2002-802623	20021010
RU 2301228	C2	20070620	RU 2004-117594	20021010
ES 2277623	T3	20070716	ES 2002-802623	20021010
MX 2004PA04307	A	20040811	MX 2004-PA4307	20040506
US 20040254175	A1	20041216	US 2004-495254	20040510
US 7199133	B2	20070403		
ZA 2004004549	A	20050204	ZA 2004-4549	20040608

PRIORITY APPLN. INFO.: DE 2001-10155075 A 20011109
WO 2002-EP11349 W 20021010

OTHER SOURCE(S): MARPAT 138:385436
GI



I

II

III

AB Title compds. I [E = (un)substituted aryl, heteroaryl; W = C(R2)2, [C(R2)2], OC(R2)2, etc.; R2 = H, A, [C(R3)2]n, etc.; R3 = H, A; X = CONR2, CONR2C(R3)2, C(R3)2NR2, etc.; Y = alkylene, cycloalkylene, Ar-diyl (sic), etc.; Ar = (un)substituted Ph, naphthyl, biphenyl; T = (un)substituted (CH2)p, e.g., N, O, S; n = 0-2; p = 1-6] and their pharmaceutically acceptable salts were prepared For example, Raney-Nickel mediated reduction of oxadiazol II, e.g., prepared from 4-nitroaniline in 4-steps, afforded isothiazolidine III acetate. In blood-coagulation factor Xa inhibition studies, isothiazolidine III acetate exhibited an IC50 value of 3.5 x 10-7 M. Compds. I are claimed useful for the treatment of thromboembolic diseases and tumors.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 32 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:133044 HCAPLUS Full-text
DOCUMENT NUMBER: 138:187647
TITLE: Preparation of phenyl derivatives as coagulation factor Xa inhibitors
INVENTOR(S): Dorsch, Dieter; Cezanne, Bertram; Tsaklakidis, Christos; Mederski, Werner; Gleitz, Johannes; Barnes, Christopher
PATENT ASSIGNEE(S): Merck Patent GmbH, Germany
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003013531	A1	20030220	WO 2002-EP7798	20020712

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

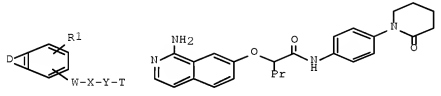
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,

CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10139060	A1	20030220	DE 2001-10139060		20010808
CA 2456717	A1	20030220	CA 2002-2456717		20020712
AU 2002325882	A1	20030224	AU 2002-325882		20020712
AU 2002325882	B2	20070517			
EP 1414456	A1	20040506	EP 2002-760242		20020712
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
BR 2002011737	A	20040928	BR 2002-11737		20020712
CN 1538845	A	20041020	CN 2002-815482		20020712
HU 2004001405	A2	20041228	HU 2004-1405		20020712
JP 2005501075	T	20050113	JP 2003-518540		20020712
MX 2004PA01121	A	20040520	MX 2004-PA1121		20040204
US 20040235828	A1	20041125	US 2004-486238		20040209
ZA 2004001800	A	20050204	ZA 2004-1800		20040304
PRIORITY APPLN. INFO.:			DE 2001-10139060	A	20010808
			WO 2002-EP7798	W	20020712

OTHER SOURCE(S): CASREACT 138:187647; MARPAT 138:187647

GI



I II

AB Novel Ph compds. I [D = (un)saturated 3 - 4 alkylene chain, containing 1 - 2 N, O and/or S {may be substituted with halogen, A, {C(R3)2}n-Ar, {C(R3)2}n-Het1, {C(R3)2}n-cycloalkyl, OR2, N(R2)2, NO2, CN, CO2R2, CON(R2)2, NR2COA, NR2SO2A, COR2, SO2NR2, S(O)mA}; W = C(R2)2, {C(R2)2}2, OC(R2)2, NR2C(R2)2; X = CONR2, CONR2C(R3)2, C(R3)2NR2, C(R3)2NR2C(R3)2; Y = alkylene, cycloalklylene, Het-diyl, Ar-diyl; T = (un)substituted heterocycle containing 1 - 4 of N, O and/or S; A = (un)branched C1-6-alkyl {may contain O, S, CH:CH or substituted with 1 - 7 F}; R1 = H, halogen, A, OR2, N(R2)2, NO2, CN, CO2R2, CON(R2)2, {C(R3)2}nAr, {C(R3)2}n-Het, {C(R3)2}n-cycloalkyl; R2 = H, A, {C(R3)2}nAr, {C(R3)2}n-Het, {C(R3)2}n-cycloalkyl; R3 = H, A; Ar = (un)substituted Ph, naphthyl, biphenyl {may be substituted with halogen, A, OR3, N(R3)2, NO2, CN, CO2R3, CON(R3)2, NR3COA, NR3CON(R3)2, NR3SO2A, COR3, SO2N(R3)2, SOmA}; Het = (un)saturated or aromatic heterocycle (containing 1 - 4 N, O and/or S and may be substituted with halogen, A, {C(R3)2}n-Het1, {C(R3)2}n-cycloalkyl, OR2, N(R2)2, NO2, CN, CO2R2, CON(R2)2, NR2COA, NR2CON(R2)2, NR2SO2A, COR2, SO2NR2, S(O)mA); Het1 = (un)saturated or aromatic heterocycle {containing 1 - 2 N, O and/or S and may be substituted with halogen, A, OR2, N(R2)2, NO2, CN, CO2R2, CON(R2)2, NR2COA, NR2CON(R2)2, NR2SO2A, COR2, SO2NR2, S(O)mA}; halogen = Cl Br, F, I; n = 0 - 2; m = 0 - 2] are claimed. I and their pharmaceutically acceptable derivs., solvates, stereoisomers and their mixts., are inhibitors of coagulation factor Xa and can be used in the prophylaxis and/or therapy of thromboembolic diseases and in the treatment of tumors. Thus isoquinoline II was prepared from 7-hydroxyisoquinoline via O-alkylation with Me(CH2)2CHBrCO2Et, saponification, amidation with 1-(4-aminophenyl)piperidin-

2-one, isoquinoline N-oxidation, isoquinoline N-oxide amination with pyridine, and reaction with ethanolamine. II was tested for thrombin receptor binding ability [IC50 = 3.5 x 10-7 M vs. FXa; IC50 = 2.2 x 10-7 M vs. TF]. I was used in the preparation of drug formulations (injections, suppositories, solns., solvates, tablets, etc.).

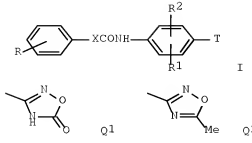
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 33 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:891946 HCAPLUS Full-text
DOCUMENT NUMBER: 139:381494
TITLE: Preparation of semicarbazides as inhibitors of blood-coagulation factor Xa and VIIa
INVENTOR(S): Mederski, Werner; Tsaklakidis, Christos; Cezanne, Bertram; Dorsch, Dieter; Barnes, Christopher; Gleitz, Johannes
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: Ger. Offen., 18 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10220048	A1	20031113	DE 2002-10220048	20020504
CA 2485065	A1	20031113	CA 2003-2485065	20030407
WO 2003093254	A1	20031113	WO 2003-EP3581	20030407
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003227569	A1	20031117	AU 2003-227569	20030407
EP 1501814	A1	20050202	EP 2003-724967	20030407
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005530754	T	20051013	JP 2004-501393	20030407
US 20050171102	A1	20050804	US 2004-513451	20041104

PRIORITY APPLN. INFO.: DE 2002-10220048 A 20020504
WO 2003-EP3581 W 20030407

OTHER SOURCE(S): MARPAT 139:381494
GI



AB Title compds. [I; R = (substituted) C(:NH)NH2, CH2NH2, CONH2, cyano, Q1, Q2; X = N(Ar)NH, NHN(Ar); Ar = (substituted) Ph; R1, R2 = H, A, OH, OA, O(CO)A, halo, CF3, CO2H, CO2A, cyano, CH2NH2, amino, NHA, NA2; A = (branched) (cyclic) C1-10 alkyl; T = (saturated) (substituted) heterocyclyl], were prepd for treating thrombosis and tumors. Thus, a mixture of 1-(3-N-hydroxyamidinophenyl)-4-[3-methyl-4-(2-oxopiperidin-1-yl)phenyl]-1-phenylsemicarbazide (preparation given), Raney-Nickel, HOAc, and H2O in MeOH was stirred over night under H2-atmosphere at room temperature followed by treatment with HCl to give 90% 1-(3-amidinophenyl)-4-[3-methyl-4-(2-oxopiperidin-1-yl)phenyl]-1-phenylsemicarbazide hydrochloride. The latter showed affinity to the receptor Xa with IC50 = 16 E-9 M and to the receptor VIIa with IC50 = 9.8 E-9 M.

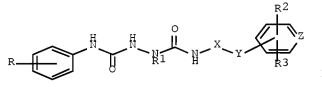
L44 ANSWER 34 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:736222 HCAPLUS Full-text
DOCUMENT NUMBER: 137:262953
TITLE: Preparation of biurethanes as inhibitors of blood-coagulation factor Xa and VIIa
INVENTOR(S): Mederski, Werner; Cezanne, Bertram ; Dorsch, Dieter; Tsaklakidis, Christos; Gleitz, Johannes; Barnes, Christopher
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002074735	A2	20020926	WO 2002-EP2095	20020227
WO 2002074735	A3	20031127		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10113402	A1	20020926	DE 2001-10113402	20010320

CA 2441427	A1	20020926	CA 2002-2441427		20020227
AU 2002253080	A1	20021003	AU 2002-253080		20020227
HU 2003003512	A2	20040128	HU 2003-3512		20020227
EP 1385818	A2	20040204	EP 2002-722151		20020227
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
CN 1498206	A	20040519	CN 2002-806758		20020227
JP 2004531494	T	20041014	JP 2002-573744		20020227
MX 2003PA08394	A	20040129	MX 2003-PA8394		20030917
US 20040097550	A1	20040520	US 2003-672084		20030917
US 6943179	B2	20050913			
ZA 2003008060	A	20040723	ZA 2003-8060		20031016
PRIORITY APPLN. INFO.:			DE 2001-10113402	A	20010320
			WO 2002-EP2095	W	20020227

OTHER SOURCE(S): MARPAT 137:262953

GI



I

AB Title compds. [I; R = H, halo, cyano; R1 = H, A, (CH2)nAr; R2 = H, halo; R3 = H, (substituted) Ph, (saturated) aromatic heterocyclyl; X = (CH2)n; Y = absent or piperidin-1,4-diyl; Z = CH, N; A = (branched) (O-, S-, CH:CH-interrupted) (fluorinated) alkyl; Ar = (substituted) Ph; n = 0-2], were prepared Thus, 1-(4-isocyanatophenyl)piperidin-2-one (preparation given) was treated with 78.4 mg N-(4-chlorophenylaminocarbonyl)-N'- phenylhydrazine followed by reflux for 2 h to give 105 mg N-(4-chlorophenylaminocarbonyl)-N'-[4-(2-oxo-1-piperidyl)phenylaminocarbonyl]-N'-phenylhydrazine. The latter showed affinity to the Xa receptor with IC50 = 180 nM/L and to the VIIa receptor with IC50 = 91 nM/L.

L44 ANSWER 35 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2002:555466 HCAPLUS Full-text
DOCUMENT NUMBER:	137:125096
TITLE:	Preparation of phenyl derivatives containing inhibitors of coagulation factor for prophylaxis and/or therapy of thromboembolic disorders
INVENTOR(S):	Dorsch, Dieter; Mederski, Werner; Tsaklakidis, Christos; Cezanne, Bertram; Gleitz, Johannes; Barnes, Christopher
PATENT ASSIGNEE(S):	Merck Patent G.m.b.H., Germany
SOURCE:	PCT Int. Appl., 133 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2002057236	A1	20020725	WO 2001-EP14296	20011205
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10102322	A1	20020725	DE 2001-10102322	20010119
CA 2434937	A1	20020725	CA 2001-2434937	20011205
AU 2002227993	A1	20020730	AU 2002-227993	20011205
AU 2002227993	B2	20070809		
EP 1351938	A1	20031015	EP 2001-989580	20011205
EP 1351938	B1	20070411		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016804	A	20040217	BR 2001-16804	20011205
CN 1518541	A	20040804	CN 2001-823061	20011205
JP 2004535362	T	20041125	JP 2002-557917	20011205
HU 2005000110	A2	20050628	HU 2005-110	20011205
AT 359271	T	20070515	AT 2001-989580	20011205
ES 2284718	T3	20071116	ES 2001-989580	20011205
MX 2003PA06483	A	20030922	MX 2003-PA6483	20030718
IN 2003KN01033	A	20060602	IN 2003-KN1033	20030813
ZA 2003006419	A	20041118	ZA 2003-6419	20030818
US 20040087582	A1	20040506	US 2003-466680	20031218
US 7273867	B2	20070925		
PRIORITY APPLN. INFO.:			DE 2001-10102322 A	20010119
			WO 2001-EP14296 W	20011205

OTHER SOURCE(S): MARPAT 137:125096

AB Novel compds. of the formula R1R2C6H3-W-X-Y-T in which W, X, Y, T, R1 and R2 are as defined in Patent Claim 1, are inhibitors of coagulation factor Xa and can be employed for the prophylaxis and/or therapy of thromboembolic disorders. Thus, 3-(5-methyl-1,2,4-oxadiazol-3-yl)phenol wa reacted with Et 2-bromovalerate, sodium hydroxide, thionyl chloride, 4-morpholin-4-ylaniline, followed a hydrogenation in acetic acid to give 2-(3-amidinophenoxy)-N-(4-morpholin-4-ylphenyl)valeramide acetate, showing IC50=3x10-7 M and IC50=4.9x10-7 M.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 36 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2002:465965 HCAPLUS Full-text
DOCUMENT NUMBER:	137:47128
TITLE:	Preparation of of ureido- and carbamoyloxy-substituted amides as inhibitors of factor Xa for the treatment of clotting disorders and tumors.
INVENTOR(S):	Dorsch, Dieter; Mederski, Werner; Tsaklakidis, Christos; Cazanne, Bertram; Gleitz, Johannes; Barnes, Christopher
PATENT ASSIGNEE(S):	Merck Patent G.m.b.H., Germany
SOURCE:	PCT Int. Appl., 92 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	German
FAMILY ACC. NUM. COUNT:	1

10551670

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002048099	A1	20020620	WO 2001-EP13545	20011121
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10063008	A1	20020620	DE 2000-10063008	20001216
CA 2431766	A1	20020620	CA 2001-2431766	20011121
AU 2002021881	A	20020624	AU 2002-21881	20011121
EP 1341755	A1	20030910	EP 2001-270524	20011121
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016115	A	20031223	BR 2001-16115	20011121
HU 2003003296	A2	20040128	HU 2003-3296	20011121
HU 2003003296	A3	20060428		
JP 2004515538	T	20040527	JP 2002-549632	20011121
NO 2003002695	A	20030613	NO 2003-2695	20030613
MX 2003PA05342	A	20031006	MX 2003-PA5342	20030613
US 20040038858	A1	20040226	US 2003-450651	20030616
IN 2003KN00896	A	20050311	IN 2003-KN896	20030714
ZA 2003005455	A	20040826	ZA 2003-5455	20030715
US 20050137230	A1	20050623	US 2005-59655	20050217

PRIORITY APPLN. INFO.: DE 2000-10063008 A 20001216
WO 2001-EP13545 W 20011121
US 2003-450651 A3 20030616

OTHER SOURCE(S): MARPAT 137:47128

AB DNHCOXCHR1CONH(CH2)nEW [D = (substituted) Ph, pyridyl; R1 = H, Ar, Het, cycloalkyl, (substituted) A; R2 = H, A; E = (substituted) phenylene, piperidin-1,4-diyl; W = Ar, Het, N(R2)2, R2, cycloalkyl; X = NH, O; A = (fluoro-substituted) (O-, S-, or CH:CH-interrupted) alkyl; Ar = (substituted) Ph; Het = (aromatic) (substituted) heterocyclyl; n = 0, 1], were prepared Thus, Z-D-Phe-OH, 2'-methylsulfonylbiphenyl-4-ylamine, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole, and 4-methylmorpholine were stirred 40 h in DMF to give benzyl [(R)-1-(2'-methylsulfonylbiphenyl-4-ylcarbamoyl)-2-phenylethyl]carbamate. This was hydrogenolyzed in MeOH over Pd/C and the product was stirred with 4-chlorophenyl isocyanate in CH2Cl2 to give (R)-2-[3-(4-chlorophenyl)ureido]-N-(2'-methylsulfonylbiphen-4-yl)-3-phenylpropionamide. The latter inhibited factor Xa with IC50 = 8.6 + 10-8 M.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 37 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:791975 HCAPLUS Full-text

DOCUMENT NUMBER: 137:310701

TITLE: Preparation of ethanediamides as inhibitors of blood coagulation factor Xa for the treatment of thromboembolic illnesses

INVENTOR(S): Mederski, Werner; Cezanne, Bertram ; Dorsch, Dieter; Tsaklakidis, Christos; Gleitz, Johannes; Barnes, Christopher

PATENT ASSIGNEE(S): Merck Patent GmbH, Germany
SOURCE: Ger. Offen., 34 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10117823	A1	20021017	DE 2001-10117823	20010410
CA 2445538	A1	20021024	CA 2002-2445538	20020318
WO 2002083630	A1	20021024	WO 2002-EP2963	20020318
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002308166	A1	20021028	AU 2002-308166	20020318
EP 1377543	A1	20040107	EP 2002-761892	20020318
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
HU 2003003733	A2	20040301	HU 2003-3733	20020318
CN 1514823	A	20040721	CN 2002-811605	20020318
US 20040220411	A1	20041104	US 2003-474969	20031016
BR 2003004917	A	20050614	BR 2003-4917	20031016
ZA 2003008669	A	20050207	ZA 2003-8669	20031106
MX 2003PA10205	A	20040310	MX 2003-PA10205	20031107
PRIORITY APPLN. INFO.:			DE 2001-10117823 A	20010410
			WO 2002-EP2963 W	20020318

OTHER SOURCE(S): MARPAT 137:310701
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1, R3 = H, aryl, aryl-alkyl, etc.; R2 = aryl, Het; R4 = H, OH, O-aryl, etc.; X = aryl, aryl-alkyl, etc.; aryl = (un)substituted Ph, naphthyl, biphenyl; Het = (un)substituted aromatic heterocyclic with 1-4 N, O and/or S atoms; with provisos], their pharmaceutically acceptable salts and formulations were prepared For example, Ra-Ni/H2 reduction of oxadiazole II, prepared from 3-[3-(bromomethyl)phenyl]-5-methyl-1,2,4- oxadiazole in 6-steps, followed by amine deprotection afforded carboximidamide III.TFA. In inhibition studies of blood coagulation factor Xa, 7-specific examples of I exhibited IC50 values ranging from 6.0 μM - 9.6 nM, e.g., IC50 of carboximidamide III.TFA = 10 nM. Approx. 71-specific examples of compds. I and 52-intermediates were prepared

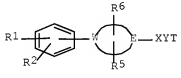
L44 ANSWER 38 OF 38 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:714060 HCAPLUS Full-text
DOCUMENT NUMBER: 137:232677
TITLE: Preparation of heterocyclylphenyls for treatment of thromboembolic diseases and tumors

INVENTOR(S): Mederski, Werner; Ceranna, Bertram ; Dorsch, Dieter; Tsaklakidis, Christos; Gleitz, Johannes; Barnes, Christopher
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: Ger. Offen., 28 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10112768	A1	20020919	DE 2001-10112768	20010316
CA 2440954	A1	20020926	CA 2002-2440954	20020227
WO 2002074765	A1	20020926	WO 2002-EP2092	20020227
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002249246	A1	20021003	AU 2002-249246	20020227
EP 1368341	A1	20031210	EP 2002-718165	20020227
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
HU 2003003539	A2	20040128	HU 2003-3539	20020227
CN 1496361	A	20040512	CN 2002-806536	20020227
JP 2004527514	T	20040909	JP 2002-573774	20020227
MX 2003PA08216	A	20040129	MX 2003-PA8216	20030911
US 20040082563	A1	20040429	US 2003-471768	20030916
ZA 2003008028	A	20050117	ZA 2003-8028	20031015

PRIORITY APPLN. INFO.: DE 2001-10112768 A 20010316
WO 2002-EP2092 W 20020227

OTHER SOURCE(S): MARPAT 137:232677
GI



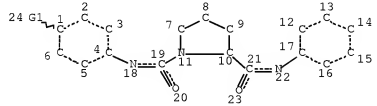
I

AB Title compds. [I; R1 = H, cyano, (substituted) C(:NH)NH2, CON(R3)2, [C(R4)2]nN(R3)2, etc.; R2, R5, R6 = H, halo, A, OR3, N(R3)2, NO2, cyano, [C(R4)2]nAr, [C(R4)2]nHet, [C(R4)2]ncycloalkyl, etc; R3 = H, A, [C(R4)2]nAr, [C(R4)2]nHet, [C(R4)2]ncycloalkyl; R4 = H, A; W = N, CR3; EW = 3-7 membered (substituted) (saturated) (benzo-, heterocyclyl-condensed) (hetero)cyclyl; X = [C(R4)2]nCONR3[C(R4)2]n, [C(R4)2]nNR3CO[C(R4)2]n, etc; Y = alkylene, cycloalkylene, heterocyclyldiyl, aryldiyl; T = (substituted) (bi)heterocyclyl; A = (branched) (O-, S-, CH:CH-interrupted) (fluorinated) C1-6 alkyl; Ar = (substituted) Ph, naphthyl, biphenyl; Het = (substituted) (aromatic)

(bi)heterocyclyl; n = 0-2], were prepd as inhibitors of factor Xa and VIIa (no data). Thus, a mixture of 4-(tert-butoxycarbonyl)-1-(3-cyanophenyl)piperazine-2-carboxylic acid, 1-(4-aminophenyl)piperidin-2- one, N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride, and hydroxybenzotriazole hydrate in DMF was stirred with 4-methylmorpholine for 18 h at room temperature to give 4-(3-cyanophenyl)-3-[4-(2-oxopiperidin-1-yl)phenylcarbamoyl]piperazine-1-carboxylic acid tert-Bu ester which was stirred with DMSO, K2CO3, and H2O2 in MeOH for 2 h at room temperature to give (3-carbamoylphenyl)-3-[4-(2-oxopiperidin-yl)phenylcarbamoyl]piperazine-1-carboxylic acid tert-Bu ester. The latter was treated with HCl in dioxane for 1 h to give 1-[(3-carbamoylphenyl)-piperazin-2-yl]-N-[4-(2- oxopiperidin-1-yl)phenyl]amide.

```
=> dis his nofile

     (FILE 'HOME' ENTERED AT 15:33:08 ON 18 JUN 2008)

     FILE 'REGISTRY' ENTERED AT 15:33:26 ON 18 JUN 2008
L1               STR
L2            50 SEA SSS SAM L1
L3               STR L1
L4            47 SEA SSS SAM L3
L5           746 SEA SSS FUL L3
               D L5 QUE STAT

     FILE 'HCAPLUS' ENTERED AT 15:37:04 ON 18 JUN 2008
L6            16 SEA ABB=ON  PLU=ON  L5/P
               D 1-16 IBIB ABS HITSTR

     FILE 'REGISTRY' ENTERED AT 15:39:04 ON 18 JUN 2008
               D L5 QUE STAT

     FILE 'HCAPLUS' ENTERED AT 15:39:04 ON 18 JUN 2008
               D L6 1-16 IBIB ABS FHITSTR

     FILE 'REGISTRY' ENTERED AT 15:40:22 ON 18 JUN 2008
L7               STR
L8               STR
L9            42 SEA SSS SAM L7
L10           50 SEA SSS SAM L8

     FILE 'CASREACT' ENTERED AT 15:41:29 ON 18 JUN 2008
L11              STR L7
L12           0 SEA SSS SAM L11 (     0 REACTIONS)
L13           5 SEA SSS FUL L11 (    10 REACTIONS)
               D L13 QUE STAT
               D 1-5 IBIB ABS FHIT

     FILE 'MEDLINE, BIOSIS, EMBASE, HCAPLUS' ENTERED AT 15:45:51 ON 18 JUN 2008
L14            9 SEA ABB=ON  PLU=ON  MEDERSKI W?/AU
L15           43 SEA ABB=ON  PLU=ON  MEDERSKI W?/AU
L16           21 SEA ABB=ON  PLU=ON  MEDERSKI W?/AU
L17          144 SEA ABB=ON  PLU=ON  MEDERSKI W?/AU
     TOTAL FOR ALL FILES
L18          217 SEA ABB=ON  PLU=ON  MEDERSKI W?/AU
L19            2 SEA ABB=ON  PLU=ON  TSAKLAKIDIS C?/AU
L20           17 SEA ABB=ON  PLU=ON  TSAKLAKIDIS C?/AU
```

```
L21             2 SEA ABB=ON  PLU=ON  TSAKLAKIDIS C?/AU
L22            78 SEA ABB=ON  PLU=ON  TSAKLAKIDIS C?/AU
     TOTAL FOR ALL FILES
L23            99 SEA ABB=ON  PLU=ON  TSAKLAKIDIS C?/AU
L24            11 SEA ABB=ON  PLU=ON  DORSCH D?/AU
L25            47 SEA ABB=ON  PLU=ON  DORSCH D?/AU
L26            16 SEA ABB=ON  PLU=ON  DORSCH D?/AU
L27           185 SEA ABB=ON  PLU=ON  DORSCH D?/AU
     TOTAL FOR ALL FILES
L28           259 SEA ABB=ON  PLU=ON  DORSCH D?/AU
L29             4 SEA ABB=ON  PLU=ON  CEZANNE B?/AU
L30            10 SEA ABB=ON  PLU=ON  CEZANNE B?/AU
L31             4 SEA ABB=ON  PLU=ON  CEZANNE B?/AU
L32            48 SEA ABB=ON  PLU=ON  CEZANNE B?/AU
     TOTAL FOR ALL FILES
L33            66 SEA ABB=ON  PLU=ON  CEZANNE B?/AU
L34            26 SEA ABB=ON  PLU=ON  GLEITZ J?/AU
L35            39 SEA ABB=ON  PLU=ON  GLEITZ J?/AU
L36            31 SEA ABB=ON  PLU=ON  GLEITZ J?/AU
L37            83 SEA ABB=ON  PLU=ON  GLEITZ J?/AU
     TOTAL FOR ALL FILES
L38           179 SEA ABB=ON  PLU=ON  GLEITZ J?/AU
L39             2 SEA ABB=ON  PLU=ON  L14 AND L19 AND L24 AND L29 AND L34
L40             6 SEA ABB=ON  PLU=ON  L15 AND L20 AND L25 AND L30 AND L35
L41             2 SEA ABB=ON  PLU=ON  L16 AND L21 AND L26 AND L31 AND L36
L42            34 SEA ABB=ON  PLU=ON  L17 AND L22 AND L27 AND L32 AND L37
     TOTAL FOR ALL FILES
L43            44 SEA ABB=ON  PLU=ON  L18 AND L23 AND L28 AND L33 AND L38
L44            38 DUP REM L43 (6 DUPLICATES REMOVED)
                  D 1-38 IBIB ABS

=> d l5 que stat;d l13 que stat
L3                STR
```



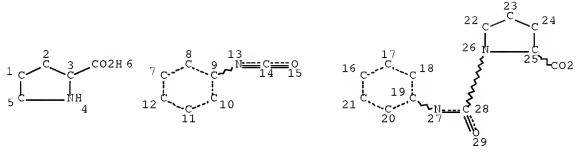

```
VAR G1=X/25
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
```

RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 26

STEREO ATTRIBUTES: NONE
L5 746 SEA FILE=REGISTRY SSS FUL L3

100.0% PROCESSED 1364 ITERATIONS 746 ANSWERS
SEARCH TIME: 00.00.01

L11 STR



Page 1-A

H 30

Page 1-B
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 30

STEREO ATTRIBUTES: NONE
L13 5 SEA FILE=CASREACT SSS FUL L11 (10 REACTIONS)

100.0% DONE 117 VERIFIED 10 HIT RXNS 5 DOCS
SEARCH TIME: 00.00.01

=> log y

STN INTERNATIONAL LOGOFF AT 15:47:08 ON 18 JUN 2008